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Original Research Article

Clinicopathological profile of primary ovarian carcinomas

Hareesh Chandran[1,*], Indu R Nair[1], Anupama R[2], Viral Patel[2]

[1]*Dept. of Pathology, Amrita Institute of Medical Sciences, Kochi, Kerala, India*
[2]*Dept. of Gynecologic Oncology, Amrita Institute of Medical Sciences,, Kochi, Kerala, India*

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ABSTRACT

Background: Ovarian cancer is the sixth most common cancer worldwide and seventh most common cause of cancer mortality. Latest WHO classification (2014) classified ovarian carcinomas into serous, mucinous, endometrioid, clear cell, Brenner, poorly differentiated / undifferentiated carcinomas and carcinosarcomas. Shih and Kurman had first proposed classifying epithelial ovarian carcinomas into Type 1 and Type 2 based on the 2 main pathways of tumorigenesis.

Objectives : To classify primary ovarian carcinomas into type 1 and type 2 based on morphology and assessment of IHC expression in different types of ovarian carcinomas. To correlate the 2 subtypes with clinical parameters and prognosis.

Materials and Methods : Retrospective observational cohort analysis of 96 cases diagnosed as primary ovarian carcinomas was done including pathologically proven primary ovarian carcinoma between April 2013 and March 2016. We collected data from hospital information system, used 5 immunohistochemical markers to classify the tumors & then followed up the patients.

Results: We found statistical significant difference for patient age, patient stage, CA125, type of surgery (IDS/PDS) between type 1 and type 2 tumors. There was a significant reduction in mean overall and progression free survival for patients with type 2 carcinomas, residual disease post surgery, higher stage & those which underwent debulking ($p<0.05$).

Conclusion: From our study we would like to conclude that, the classification of primary ovarian carcinomas into type 1 and 2 can be done based on morphological features and immunohistochemical markers comprising ER, PR, WT1, p53 & Napsin A. Frequency data of types of tumors, stage in our population concords with that of other studies in world literature. Type 2 carcinomas showed higher patient age, more advanced stage, higher CA125 levels & comprised higher proportion of cases that underwent interval debulking (post NACT) than type 1 carcinomas. Type 2 carcinomas have both lower overall and progression free survival in our study population.

1. Introduction

Ovarian carcinomas were conventionally classified based on morphology into different subtypes, but there is marked overlap in the behaviour and prognosis of these entities. Shih and Kurman had first proposed classifying epithelial ovarian carcinomas into Type 1 and Type 1 based on the 2 main pathways of tumorigenesis.[1,2] Type I tumors tend to be low-grade neoplasms that arise in a stepwise manner from borderline tumors whereas type II tumors are high-grade neoplasms for which morphologically recognizable precursor lesions have not been identified, so-called de novo development. As serous tumors are the most common surface epithelial tumors, low-grade serous carcinoma is the prototypic type I tumor and high grade serous carcinoma is the prototypic type II tumor. In addition to low-grade serous carcinomas, type I tumors are composed of mucinous carcinomas, endometrioid carcinomas, malignant Brenner

* *Corresponding author*.
E-mail address: hareesh0300@gmail.com (H. Chandran).

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tumors, and clear cell carcinomas. Type I tumors are associated with distinct molecular changes that are rarely found in type II tumors, such as BRAF and KRAS mutations for serous tumors, KRAS mutations for mucinous tumors, and beta-catenin and PTEN mutations and microsatellite instability for endometrioid tumors. Type II tumors include high-grade serous carcinoma, malignant mixed Mullerian tumors (carcinosarcoma),and undifferentiated carcinoma. There are very limited data on the molecular alterations associated with type II tumors except frequent p53 mutations in high-grade serous carcinomas and malignant mixed Mullerian tumors (carcinosarcomas). A panel of immunohistochemical markers can serve as surrogate markers for subtyping of these tumors. Hence, it can be used to categorize these tumors into types I & II. The main purpose of such a classification lies on the different prognostic and therapeutic implications of the 2 subtypes.

2. Materials and Methods

Retrospective observational cohort analysis of cases diagnosed as primary ovarian carcinomas was done.

2.1. Inclusion criteria

Was pathologically proven primary ovarian carcinoma between April 2013 and March 2016.

2.2. Exclusion criteria

Tumor specimens with torsion, where a definite diagnosis is not possible. Blocks of tumors which were damaged, missing or of poor quality.

2.3. Procedure followed

The tumor blocks were cut into thin slices (4 micrometer) using a microtome and they were stained with H&E (hematoxylin & eosin) and remaining sections were further processed for antigen retrieval, and then stained using immunohistochemical stains ER,PR,WT1, p53 and Napsin A. Data of patients were retrieved by using Hospital Information system (AHIS) database. Data included earliest hospital visit, stage of disease, surgery type (IDS/PDS), residual post surgery (RO/R1-R2) & CA125 levels which were obtained from the discharge summaries & operative notes.

2.4. Statistical analysis and results

Sample size was calculated to be 65. A total of 99 cases were obtained for the study, out of which 96 had complete follow up details. 5 panel immunohistochemistry was performed in each of the 99 cases. Out of the 3 cases without complete follow up, 2 were of patients being treated in foreign countries and remaining single patient who died due to unrelated cause.

3. Results and Observations

Total sample size -96

Table 1: Frequency (n=96)

Variables	Category	Frequency
Type 1 (Total=32) 33.3%	LGSC	12(12.5%)
	LGEC	2(2.1%)
	Mucinous	5(5.2%)
	Clear cell	13(13.5%)
Type 2 (Total=64) 66.7%	HGSC	56(58.3%)
	HGEC	6(6.3%)
	CS	2(2.1%)
Stage (Both type 1 & 2 together)	I	28(29.2%)
	II	13(13.5%)
	III	46(47.9%)
	IV	9(9.4%)
Residual disease after surgery	R0	72(75%)
	R1/R2	24(25%)
Type of surgery (Primary or interval debulking)	PDS	71(73.9%)
	IDS	25(26.1%)

The mean age of all the patients was 52.7± 11.97 years. The mean age in type 1 is 47.50 ± 13.65 and type 2 is 55.22 ± 10.10 years with a statistically significant difference (p=0.002) between the two. Median age was found to be 52.0 years.

We found statistical significant difference (table-2) for patient age, patient stage, CA125, type of surgery (IDS/PDS) between type 1 and type 2 tumors. There was a Significant reduction in mean overall and progression free survival for patients with type 2 carcinomas, residual disease post surgery, higher stage & those which underwent debulking on univariate analysis. Multivariate analysis showed stage to be the significant factor for determining progression free survival (p=<0.001), while residual post surgery (R1/R2) and type of surgery(IDS) showed significance for affecting overall survival (p<0.05).

4. Discussion

Our study highlights the importance of classifying primary ovarian carcinomas based on morphology and immunohistochemistry into different subtypes. These along with other parameters like stage, CA125 levels, residual disease post surgery, type of surgery (interval or primary debulking) can predict the prognosis & survival in these patients, which helps in better patient care.

4.1. Demographic comparison of the two groups-type 1 and type 2

We had patients ranging from 18 to 84 years. Curiously, low age at presentation was noted in certain low grade (type 1 tumors) like mucinous carcinomas in 2 patients aged 18 and 20; & 2 low grade serous carcinomas in patients aged 18 & 28. Literature available currently states

Table 2: Impact of Factors on Progression free survival

Variable	Category	Mean (in months)	Standard error	p value	Hazard ratio	95% CL	
						lower	upper
Type	1	50.28	5.35	0.011	2.299	1.184	4.463
	2	31.53	2.76				
Residual	R0	39.88	2.62	0.006	2.196	1.233	3.913
	R1/R2	27.29	6.07				
Age (in years)	≤52	37.52	3.91	0.838	-	-	-
	>52	36.37	3.63				
Stage	I/II	48.11	3.04	<0.001	3.555	1.925	6.566
	III/IV	27.97	3.55				
Type of surgery	PDS	40.79	2.88	0.001	2.480	1.435	4.287
	IDS	24.88	4.32				

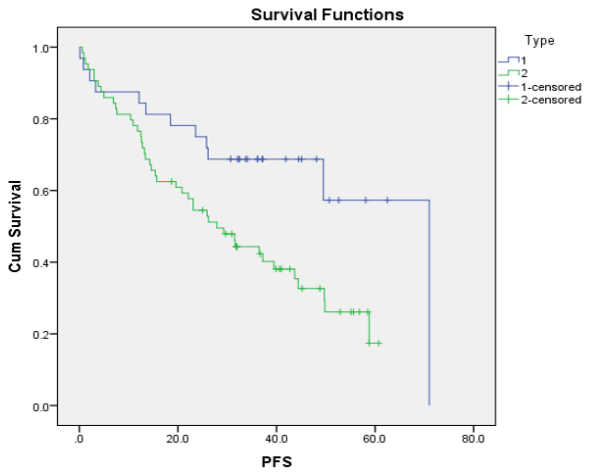

Fig. 1: Type 2 carcinomas showed lower progression free survival than type 1 carcinomas.

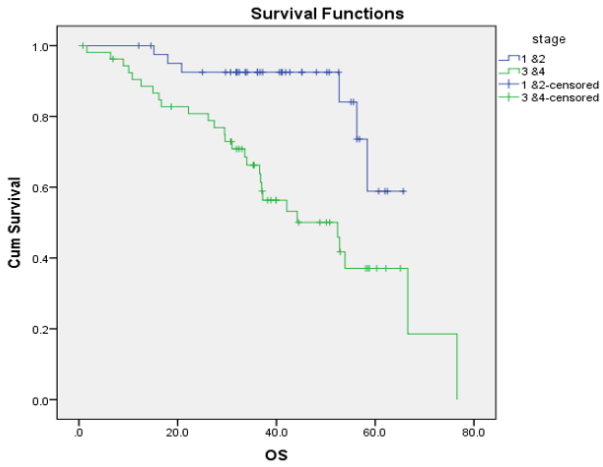

Fig. 2: Higher stage carcinomas (3 & 4) showed lower overall survival than lower stage carcinomas(1 & 2).

mucinous carcinomas to have a mean age of 45.[1] Following table compares the median age of each morphological subtype of carcinomas of our study done by Prat J.[3] Age is comparable in all except high grade serous carcinomas & carcinosarcomas which showed lower median age in our study.

4.2. Clinical parameters

Study by Keith Y.Terada et al,[4] showed that a significantly greater proportion of patients with type 1 cancer were diagnosed with stage I/II, than type 2 patients(57.8% vs 15.2%,p<0.001). We got comparable results in our study, 62.5% of type 1 cancer were diagnosed with stage I/II than type 2 patients (62.5% vs 34.4%,p=0.009). We found type 2 carcinomas to have higher stage of presentation, This concords with studies by Ie-Ming Shih and Robert J. Kurman.[5,6] Type 2 tumors, predominantly being higher stage, also showed higher CA125 values with 56.3% of cases having CA125 >500 in comparison to only 25% in type 1.Studies have shown advanced stage disease to usually have elevated CA125 levels, around 500-1000 U/mL.[7–10]

Type 2 carcinomas showed higher proportion of residual disease post surgery, through not statistically significant. The study[11] by Alexander Melamed et al from Massachusetts General Hospital revealed no association between residual disease status among histological subtypes of ovarian cancer(p=0.32). We had obtained a similar non significant p value of 0.317.

More type 2 carcinomas (34.4%) underwent interval debulking (IDS) as a group compared to type 1(9.4%). Type 1 carcinomas comprised higher proportion of cases that underwent primary debulking surgery(PDS). Study by Makar AP et al showed no evidence that NACT-IDS is superior to PDS. It states that clinical status, tumor biology, and chemosensitivity should be taken into account as type 1 tumors with favorable prognosis are less chemosensitive, and omitting optimal PDS will lead to less favorable outcome. For patients with type 2 carcinoma associated with severe comorbidity or low performance status, NACT-IDS is

the preferred option.

4.3. Morphology & Immunohistochemistry

Recent articles and literature including latest WHO(2014) have indicated the relevance of immunohistochemistry to type different ovarian carcinomas. Our study maps those of already indicated values in the WHO manual. While, Napsin A was also found to be ideal for ovarian clear cell carcinomas with a sensitivity of 69.2% in comparison to 83% obtained by Yoriko Yamashita et al.[12] Napsin A was found to be highly specific (100%) for ovarian clear cell carcinomas confirming. This is in accordance with this study. High grade serous carcinomas were found to express p53, either diffuse or total absent expression serves as a surrogate for Tp53 mutation. Positivity of this IHC helped differentiate high grade from low grade serous carcinoma in accordance with other studies.[13–17] All poorly differentiated carcinomas and carcinosarcomas showed aberrant p53 expression. In carcinosarcomas, both the carcinomatous & sarcomatous components showed aberrant p53 expression. Both high and low grade serous carcinoma expressed WT1 marker, indicating a mesothelial origin for the tumors, which is the de facto surface epithelium of the ovary.

WT1 was positive is 100 percent of high and low grade serous carcinomas, with No other tumor expressing it in our study compared to 100% of low grade serous carcinomas and 92% of high grade serous carcinoma by Prat J.[17] Endometrioid carcinoma showed high expression of hormonal receptor ER(62.5%),PR was seen in only 25% of cases,WT1 was negative in all cases. This result may not be comparable with other studies as our cases of endometrioid carcinoma included predominantly high grade endometrioid carcinoma (6 out of 8)*. Other studies have shown 86%,72% positivity each for ER & PR respectively, and negativity for WT1 for endometrioid carcinoma.[17,18] As the number of mucinous carcinomas** in our study was low (only 5 cases), the IHC expression of these cases may not be statistically significant to be compared to other studies.

Immunohistochemistry was found to be extremely useful to categorise the tumors, and to subtype them to type I & type II. The study by Okuda T et al showed p53 mutation to affect prognosis in endometrioid cancer and not in clear cell carcinoma of ovary.[19]

Our study showed high grade serous carcinoma to be the commonest tumor comprising 57 out of 96 (58.3%), second commonest included clear cell carcinoma which comprised 13 of 96 tumors (13.5%). The study by Ferlay J et al showed high grade serous carcinoma to comprise majority of newly diagnosed ovarian carcinomas,[20] while studies indicated the clear cell carcinomas to comprise 1-12% of epithelial ovarian carcinomas in North America and Europe[21–23] & 15- 25% in Japan.[24–27] Among Asian women living in the United States, CCC was Diagnosed twice as frequently (11.1%),which is comparable to our incidence. White women had shown lower CCC incidence of 4.8%.[28] Clear cell carcinomas are known to arise in a setting of endometriosis, the other commonest tumor arising from endometriosis being endometrioid carcinoma. We had a case that showed both mixture of clear cell and endometrioid areas, the predominant area being endometrioid. This patient alsohad a history of endometriosis. These findings lend credence to already available literature suggesting common origin from endometriosis, of both endometrioid and clear cell carcinomas.[1]

Other tumors included 12 cases of LGSC, 2 cases of low grade endometrioid, 4 cases of mucinous carcinoma, 6 cases of HGEC & 2 carcinosarcomas. LGSC comprised 17.4 % of serous carcinomas, while study by Kobel M et al showed it to be only 5%[29] & Prat J <5%.[30] Incidence of mucinous, endometrioid and carcinosarcoma in our study maps that of Prat J with values comprising 5.2%, 8.4%, 2.1% respectively compared to 3%, 10%, 2 % by Prat J.[30] Regarding the incidence of low and high grade serous carcinomas, studies[15,16] indicated lower frequency of prototypic type 1 tumors, ie, low grade serous carcinoma(25%) than the prototypic type 2 tumors, ie, high grade serous carcinoma(75%). While our study showed low grade serous carcinomas to comprise 17.4% and high grade serous carcinomas comprising 82.6% of all serous carcinomas.

Most of our cases presented with high stage disease (III/IV) comprising 57%. The study from Netherlands[31] showed upto 70% of newly diagnosed ovarian carcinomas to comprise high stage disease. We had 72 cases with optimal debulking during surgery, 8 cases with <1 cm tumor remaining (R1) and rest with larger residual disease (R2). 71 cases underwent primary debulking (PDS), while 25 cases had interval debulking (post neoadjuvant chemotherapy) (IDS).

4.4. Analysis of survival data

Overall, our study confirms the findings of Shih and Kurman[15,16] based on their study on patients from John Hopkins hospital, USA and that of Sehdev et al.[32] Their studies showed prototypic type 1 tumor, LGSC to be indolent with slow progression and a 5-year survival of 55%, & prototypic type 2 tumor, HGSC to be more aggressive, with rapid progression and 5- year survival of 30%. Our study compared both progression free survival and overall survival for both type 1 and type 2 carcinomas, which showed type 2 (high grade) tumors to have much worse overall survival (p=0.042,Hazard ratio=2.593) & progression free survival (p=0.011, Hazard ratio=2.299)(Figure 1). Thus, indicating much worse prognosis for type 2 carcinomas. Study by Chen X et al[7] showed overall and progression free survival durations of patients with type 1 ovarian cancer to be longer than those of patients with type

2 ovarian cancer(p<0.001,p<0.001respectively). The table which follows compares our data with that of Chex X et al,[7] regarding statistical significance of the effect of type of tumor, residual post surgery and stage of disease on overall and progression free survival.

In our study, most significant predictor of worse overall survival and progression free survival seems to be stage of the disease with p value of 0.001 and <0.001 respectively on univariate analysis, & p value of <0.001 on multivariate analysis (PFS).(Figure 1) Other factors resulting in lower overall and progression free survival include residual disease post surgery (R1/R2) with p=0.001,p=0.006 respectively, along with type of surgery (interval debulking surgery) with p=0.001 for both. While IDS showed worse overall and progression free survival, this could be explained partly by them comprising more of type 2(p=0.005) and R1/R2 cases (p=0.01).

Multivariate analysis showed stage to be the significant factor for determining progression free survival (p=<0.001), while residual post surgery (R1/R2) and type of surgery(IDS) showed significance (p=0.001,p=0.003 respectively) for affecting overall survival. Studies with similar results include that of Zheng Feng et al[29] which revealed advanced FIGO stage to be a statistically significant in reducing overall survival on multivariate analysis, with a p value of 0.001, & also showed residual disease post surgery to significantly affect OS, PFS in multivariate analysis (R2 for PFS,R1 for OS).

Thus, our survival data proves that type 2 tumors, higher stage tumors, residual disease post surgery & interval debulking surgery to result in worse prognosis.

5. Conclusion

From our study we would like to conclude that, the classification of primary ovarian carcinomas into type 1 and 2 can be done based on morphological and immunohistochemical features. The immunohistochemical panel comprising ER, PR, WT1, p53 & Napsin A is apt for subtyping the primary ovarian carcinomas. Frequency data of types of tumors, stage in our population concords with that of other studies in world literature. Type 2 carcinomas showed higher patient age, more advanced stage, higher CA125 levels & comprised higher proportion of cases that underwent interval debulking (post NACT) than type 1 carcinomas. Type 2 carcinomas have both lower overall and progression free survival in our study population. Adverse factors affecting both overall and progression free survival include tumor type, suboptimal resection with residual disease post surgery (R1-R2), high stage, interval debulking type of surgery. However, the single most prognostic factor is the stage of disease.

6. Strengths & Limitations

We performed morphological and immunohistochemistry analysis to subtype and then prognosticate type 1 and 2 carcinomas. Indian studies on this aspect are too few on this aspect. While international studies have evaluated immunohistochemistry, demography and prognosis of type 1 and 2 carcinomas with many separate studies on different samples, we analysed a host of features, ie. Immunohistochemical expression, demographic data, and effect of 5 different variables on overall and progression free intervals by a single study with a defined sample size. While, our study is based on morphology and immunohistochemistry

expression, simultaneous assessment of molecular markers would have helped to ascertain the validity of the immunohistochemistry markers. Molecular markers can be used to subclassify tumors which show overlapping /ambiguous immunohistochemistry expression. Hence, a study including molecular markers (retrospective and prospective) would help better subclassification and understanding of primary ovarian carcinomas.

7. Source of Funding

No financial support was received for the work within this manuscript.

8. Conflict of Interest

The authors declare they have no conflict of interest.

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Author biography

Hareesh Chandran, Resident

Indu R Nair, Professor

Anupama R, Professor

Viral Patel, Resident

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