International Journal Of

Recent Scientific Research

ISSN: 0976-3031

Volume: 7(1) January -2016

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THE OFFICIAL PUBLICATION OF
INTERNATIONAL JOURNAL OF RECENT SCIENTIFIC RESEARCH (IJRSR)
http://www.recentscientific.com/ recentscientific@gmail.com

ISSN: 0976-3031

Available Online at http://www.recentscientific.com

International Journal of Recent Scientific Research
Vol. 7, Issue, 1, pp. 8571-8577, January, 2016

International Journal of Recent Scientific Research

RESEARCH ARTICLE

CHEMOTHERAPY INDUCED CHANGES IN THE OVARIAN TUMORS – HISTOMORPHOLOGY AS A DIAGNOSTIC AND AS A PROGNOSTIC TOOL

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ARTICLE INFO

Article History:

Received 16th October, 2015
Received in revised form 24th November, 2015
Accepted 23rd December, 2015
Published online 28th January, 2016

Key words:

Fibrosis, residue, necrosis, gynaecological malignancy.

ABSTRACT

Ovarian tumors are the second most common tumor affecting the female genital tract. Post chemotherapy, the ovarian tumors shows myriad of histomorphology and poses diagnostic challenges to the pathologists. The aim of this study is to analyse the histomorphological changes that are observed in various ovarian tumors following chemotherapy and to assess the prognosis based on the variables. During the one year study period, eleven cases were received. In majority of the cases the residual tumor size was more than five centimetre. Mild fibrosis, mild inflammatory reaction and grade I and II residual tumor was seen in majority of the patients. 45.5% of the tumor showed necrosis. Pre-treatment biopsies help in arriving at the correct diagnosis and prevent unnecessary additional investigations. Grading of fibrosis, size of the residual tumor and presence of necrosis should be mentioned in the final pathology report of the post chemotherapy specimens as they have prognostic significance.

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INTRODUCTION

Ovarian tumors are the second leading gynaecological malignancy [Khandakar B *et al*, 2015, Agarwal S *et al*, 2012,Momtahen S *et al*, 2009]. It constitutes about 3% of all the cancer and has a mortality of 5% [Jemal A *et al*, 2010]. Advanced stage at which it is diagnosed has decreased the survival rate. Chemotherapy and cytoreductive surgery are done to improve the prognosis of advanced cases that is in TNM stage III or above tumors. Cytoreduction are done as an interval procedure according to the current National Comprehensive Cancer Network guidelines -2012. Chemotherapy induces innumerable changes in the tumor morphology posing diagnostic difficulties to the pathologists. Moreover, most of the specimens are sent without pre chemotherapeutic histopathological evaluation adding on to the diagnostic challenge. As a result, detailed diagnostic workup is necessary to arrive at a diagnosis. Awareness of chemotherapy induced changes among the pathologist and pre- chemotherapy biopsies from the tumor helps to avoid such confusion.

Factors like clinical improvement, CT scan and serum CA 125 levels are useful to predict the prognosis. But they are inferior when compared to histomorphological studies as the type, grade and residual tumor tissue are more reliable prognostic factors [Aletti GD *et al*, 2007,Bodurka C D *et al*,2012].This study was done to evaluate the histomorphology of the ovarian specimens received as a part of cytoreductive surgery. Very few studies were done on this and they were done on a single type of ovarian tumor [Miller K *et al*, 2008, Sassen S *et al*, 2007]. This study was done on all the types of ovarian tumors we had encountered during the study period.

METHODS

Study period

One year from December 2014- December 2015

Inclusion criteria

Malignant ovarian tumor specimens that were sent with the history of cytoreduction were included in our study

Exclusion criteria

Specimens with the diagnosis of benign ovarian tumor

Malignant ovarian tumors that were not treated with chemotherapy

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All other tumors

Out of the 4110 gynaecological specimens that were received in our department from the tertiary care referral hospital during our study period, eleven cases were sent with the history of interval cytoreduction. Age incidence was calculated from the records and following histomorphological examinations were carried out.

Gross examination

The hysterectomy specimens we received were fixed in formalin. Uterus with cervix was measured and examined. The ovaries were weighed and measured. The capsule of the ovaries was examined for the breech. On cut surface the nature of the specimen [solid/cystic/both], tumor size, colour, consistency and the extent were noted. One block per centimetre of the tumor was taken. Unilateral/bilateral involvement in case of ovary was noted. The fallopian tubes, adnexa and the omentum were examined. The deposits in the omentum if any, was measured and bits were taken from the representative areas [Wilkinson N *et al*, 2011].

Microscopy

The haematoxylin and eosin stained sections were examined. Fibrosis [Fig 1], necrosis [Fig 2], inflammation [Fig 3],foamy macrophages [Fig 4], Psammoma bodies [Fig 5], haemorrhage, cystic changes, giant cell reaction[Fig 4] and residual tumor tissue [size and grade] were noted.

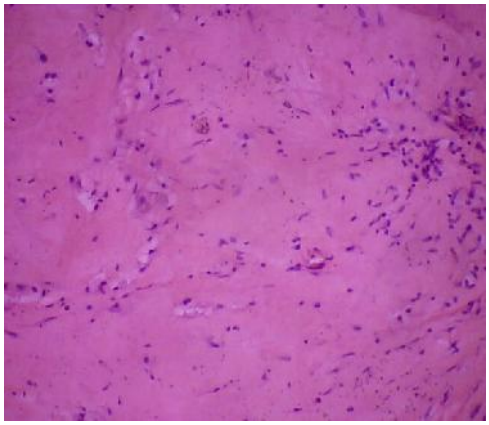

Fig 1 Shows severe fibrosis [40x, H&E]

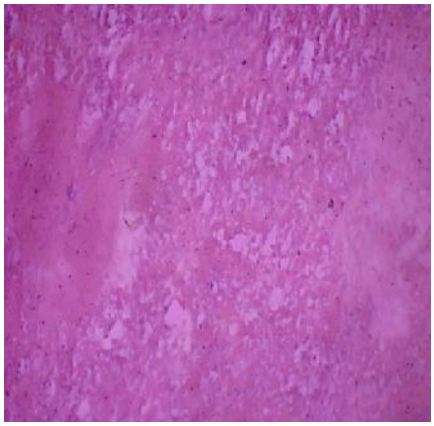

Fig 2 Shows necrosis [40x,H&E]

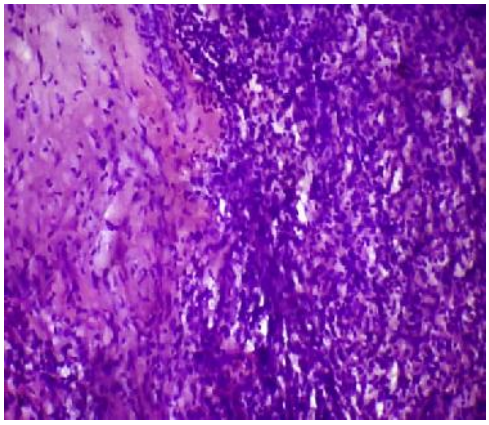

Fig 3 Shows dense inflammatory cell infiltrates

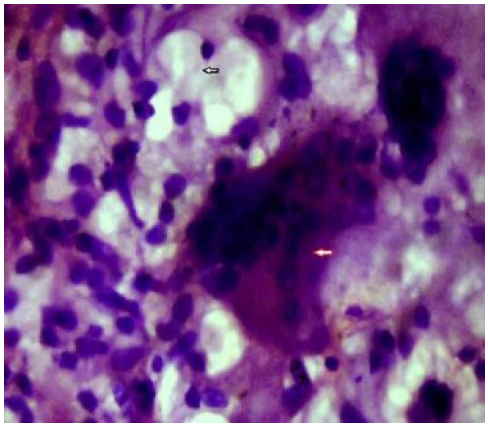

Fig 4 Shows foamy cells [black arrow] and [40x, H&E] giant cells[red arrow].[40x, H&E]

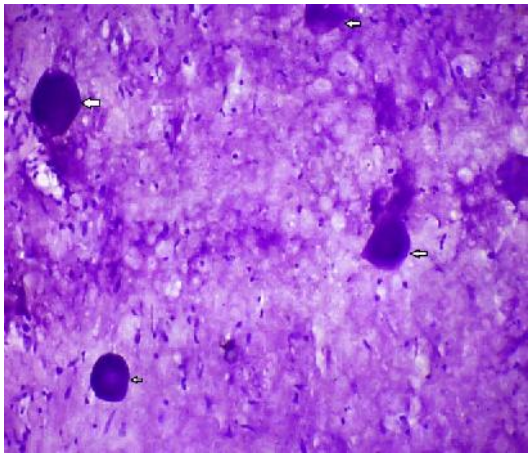

Fig 5 Shows psammoma bodies [black arrows][40x, H&E]

Fibrosis were graded as no fibrosis, mild, moderate and severe degree of fibrosis and scores 0 to 3 were given respectively. Necrosis was graded as follows: 0 score was given when there was no necrosis, 1+ was given when there were 1-50% necrotic area and 2+ was given when necrosis involve > 50% of the tumor tissue. Inflammation was scored as 0[no inflammation], 1+ [mild] and 2+ [severe]. Foamy macrophages, Psammoma bodies and cystic changes were noted if there were present. Residual tumor tissue was graded as 0 [No residual tumor], 1+[<5% tumor], 2+ [6-50%] and 3+ [>50%].This grading was based on Langer R *et al*, Wu TT *et al* and White RR *et al*' s studies. [Langer R *et al*, 2009, Wu TT *et al*, 2007, White RR *et*

al, 2005]. Based on the size of the residual tumor, microscopic tumor residue, <5cm and >5cm cut off was assigned to assess the prognosis based on Winter E W *et al*'s study [Winter E W *et al*, 2008]. Cytological changes like cytoplasmic vacuoles, abundant eosinophilic cytoplasm, bizarre nuclei, smudge nuclear chromatin, prominent nucleoli and giant cells were also noted.

When the morphology of the tumor tissue was analysed, following protocol was followed:

Non mucinous lining epithelium, papillary structures and presence of Psammoma bodies were taken as a clue for serous carcinoma [Wang Y *et al*, 2013] [Fig 6]. Angulated glands, cribriform pattern, branching pattern with nuclear stratification arranged in expansile invasive pattern were taken as a clue for endometrioid carcinoma [Chen S *et al*, 2005] [Fig 7]. Presence of clear cells and hobnail nuclear pattern was taken as clear cell carcinoma. Immunohisto chemistry was used when faced with morphological mimickers as the expressions of the immuno markers do not vary with chemotherapy [Miller K *et al*, 2008].

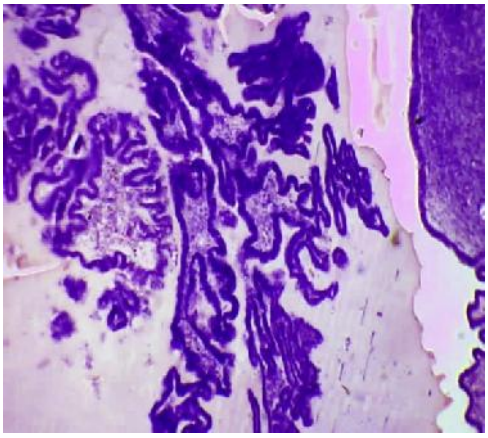

Fig 6 Shows tumor cells arranged in papillary structures- serous carcinoma [10x, H&E]

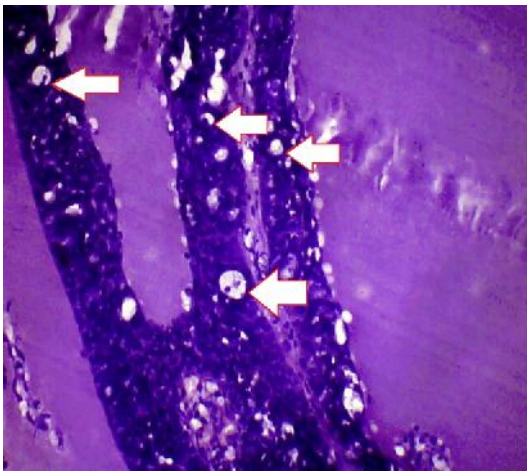

Fig 7 Shows tumor cells arranged in back to back glandular pattern. Cytoplasmic vacuoles are also noted [red arrows][10x H&E]

One case posed us a diagnostic challenge. Cytoreductive surgery was done on a 20 year old female and specimen was sent to our department. Biopsy was not taken prior to chemotherapy and she had non-functional tumor. Grossly, bilateral ovary was involved. Each ovary measured 12 cm and 8 cm respectively. The capsule was intact. On cut surface one of the ovaries was solid and cystic and the other was solid. Both were grey yellow in colour [Fig 8]. Microscopically, both the ovaries showed tumor tissue arranged in cords and nests. Individual tumor cells had abundant eosinophilic cytoplasm, dispersed chromatin and prominent nucleoli [Fig 9]. Stroma showed edema, fibrosis and haemorrhage. Provisional diagnosis was made as sex cord stromal tumor (NOS)/ poorly differentiated serous carcinoma. Immunohistochemistry was done. Inhibin and calretinin was negative [Fig 10] and cytokeratin was positive [Fig 11].

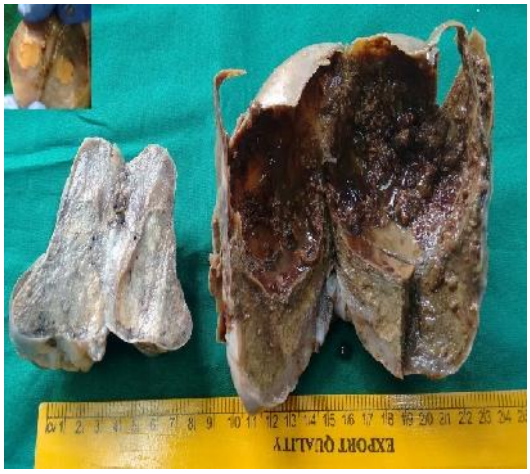

Fig 8 Shows one ovary was solid grey yellow and theovary was replaced by a solid and cystic grey yellow tumor. [Inset shows a grey yellow area]

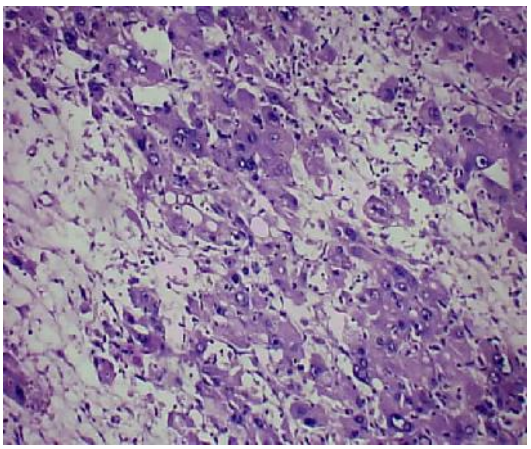

Fig 9 Shows tumor cells with abundant eosinophilic cytoplasm arranged in cords, nests and trabeculae [10x,H&E]

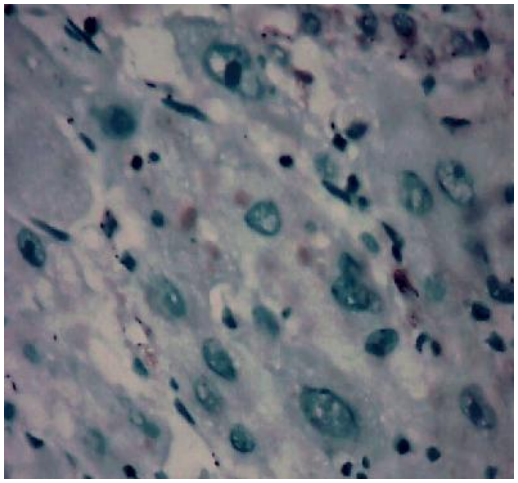

Fig 10 Shows inhibin negative tumor tissue [40x, IHC]

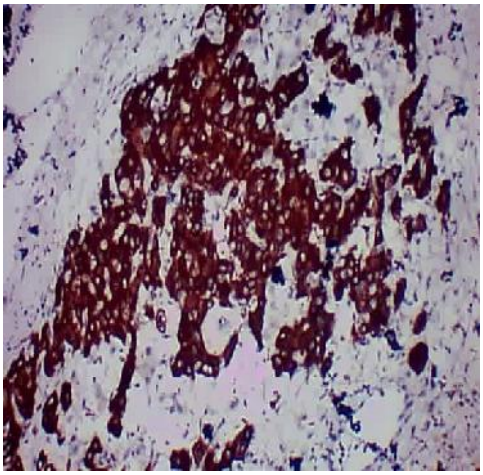

Fig 11 Shows strong cytokeratin positivite tumor cells[10x, IHC]

RESULTS

During the one year period, out of 4110 gynaecology specimens, eleven cases were sent to us with the history of cytoreduction. The incidence rate calculated from that was 0.3%.

When the age incidence was calculated, two cases were below 30 years of age. The rest were between 40 years to 65 years with the mean of 46 years [Table 1]. In Kandhakar B *et al*'s study, the mean age was 50 years which correlated with our study [Khandakar B *et al*, 2015]. Samrao D *et al* had mentioned the median age in their study population was 57 years [Samrao D *et al*, 2012].

Table 1 Age wise breakup in our study

20-30yrs	31-40yrs	41-50yrs	>50 years
18.2%	18.2%	18.2%	45.4%

When the size of the tumor was stratified most of the cases were more than five centimetres in size [Table 2]. Out of the eleven cases we analysed, three cases had no tumor residue even after extensive search.

Table 2 Size of the residual tumor

Microscopic residue	<5cm	>5cm
9%	36.4%	54.6%

When the tumors were analysed histomorphologically, mild fibrosis was noted in majority of the cases [Table 3]. Khandakar B *et al* in their study had observed fibrosis and calcification [Khandakar B *et al*, 2015]. Sassen *et al* in their study had mentioned that fibrosis is more common after neoadjuvant chemotherapy [Sassen S *et al*, 2007]. 45.5% of the cases had necrosis in our study. Mild inflammatory reaction was observed in majority of our cases. In our study, equal number of cases had grade I and II residual tumor tissue [Table3].

Table 3 Histomorphological entities and their grades

Grade	0	1+	2+	3+
Fibrosis	9%	64%	18%	9%
Necrosis	45.5%	9%	45.5%	-
Inflammation	-	91%	9%	-
Residual tumor	27.2%	36.4%	33.4%	9%

When other histomorphological changes like cystic change, haemorrhage, foamy macrophages, psammoma bodies and giant cells were analysed, haemorrhage was most commonly observed [Table4].

Table 4 Secondary changes observed in our study

Cystic changes	Haemorrhage	Foamy cells	Psammoma bodies	Giant cells	Omental deposits
64%	73%	64%	27.3%	9%	18%

Omental deposits were seen in only 18% of the cases we studied [Fig 12, 13]. Cytological changes observed in our study included eosinophilic cytoplasm, vacoulation, smudged nuclear chromatin and prominent nucleoli [Fig 14].

Fig 12 Shows omentum studded withdeposits [black arrow]

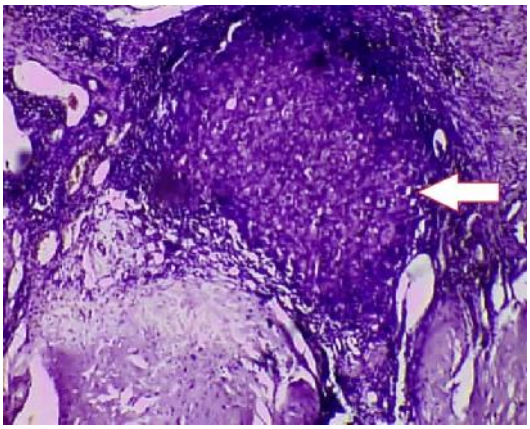

Fig 13 Shows omental deposits [red arrow] [10x H&E]

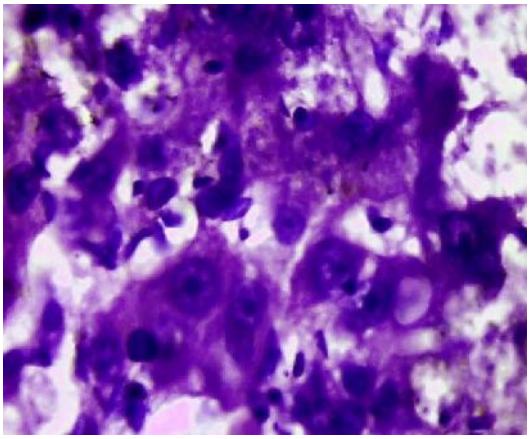

Fig 14 Shows tumor cells exhibiting abundant eosinophilic cytoplasm and prominent nucleoli- Chemotherapy effects [40x, H&E]

When the histological type was analysed, the most common variant observed was high grade serous carcinoma [Table 5].

Table 5 Histological variants observed

High grade serous carcinoma	Low grade serous carcinoma	Endometrioid carcinoma	Undifferentiated carcinoma
73%	9%	9%	9%

And an interesting case with both inhibin and calretinin negativity and positive cytokeratin marker was seen during our study period. Morphologically, the tumor showed neither papillary structures nor psammoma bodies which were seen in serous carcinoma. The cells had eosinophilic to vacuolated cytoplasm arranged in cords and nests. The stroma was edematous and showed fibrosis focally. Immunohistochemical markers like calretinin and inhibin were negative. Because the tumor was simulating sex cord stromal tumor morphologically, we reviewed the literature and found that the sensitivity of calretinin and inhibin in detecting steroid cell tumor NOS is 60% to 90% and in 5% to 90% respectively [Kim S J *et al*, 2014]. Li K, et in their study had mentioned cytokeratin, EMA and S100 expression in sex cord stromal tumor NOS [Li K *et al*, 2014]. Seidman JD, *et al* in their study had found that 46% of the sex cord stromal tumor NOS were positive for cytokeratin [Seidman JD *et al*, 1995]. Metastatic sexcord stromal tumors are negative for calretinin and inhibin [Deavers T M *et al*, 2003]. Bilateral involvement of the ovary and the malignant features seen in our case were rarely seen in sex cord stromal tumors. High serous carcinoma and undifferentiated carcinoma could not be ruled out in this case as cytokeratin was positive. Abundant cytoplasm and nuclear features exhibited by the tumor cells could be the cytopathic effect of chemotherapy. An exhaustive list of markers including WT1, AR, P53, HNF-1β, FOXL2, SF-1 and MART-1 to name a few are needed to exclude the differentials. It is impossible to do all the marker analysis in a resource poor setting due to lack funds or lack of availability of markers. The easier way around in difficult cases like ours is of course pre-treatment biopsy.

DISCUSSION

Tumors of the ovary are the second leading cause of all the gynaecological malignancies [Khandakar B *et al*, 2015, Agarwal S *et al*, 2012, Momtahen S *et al*, 2009]. Neoadjuvant chemotherapy for advanced ovarian carcinoma either as an interval procedure or after completion of chemotherapy is routinely followed [Wang Y *et al*, 2013]. Although the tumor pathology and histomorphology of ovarian tumors are well researched, few researches are done so far to study the histomorphology of the ovarian tumors following cytoreduction. Prognostic values of the variables that were observed in the post chemotherapy ovarian tumors are discussed in detail.

According to Marszalek A, *et al*'s study the age influenced the prognosis [Marszalek A *et al*, 2010]. Postmenopausal women had higher risk according their study. Khandakar B, *et al* in their study had observed that the survival was more when the age of the patients were less than fifty years [Khandakar B *et al*, 2014].

When the residual tumor size and the survival were compared between various studies following parameters were observed.In Scarabelli *et al*'s study when the size of tumor residue was <1 cm, survival was 42.2% and it was reduced to 21.3% when the size of tumor residue was >0-1 cm [Scarabelli C *et al*, 2000]. According to Chi *et al*'s study, when the residual tumor size was <1 cm, the survival percentage was 50 and it reduced to 28 when the size >1-2cm. [Chi DS *et al*, 2006]. Eisenkop, *et al* in their study had found the survival percentage as 52 when the size of the residual tumor was <1cm and it dropped to 30% when the residue was >1-2cm. [Eisenkop SM *et al*, 2003] In Marszalek A, *et al*' study, the survival percentage was 55.4% when there was no residue and if the residual size was > 1cm, the survival percentage fell up to24.2%. [Marszalek A *et al*, 2010] Gynaecologic Oncology Group [GOG] recommends that the optimal residual tumor size should be less than one cm. [Fader AN *et al*, 2007]. Winter E W, *et al* in their study had analysed the survival based on the size of the residual tumor [0.1- 1cm, 1.1-5cm and more than 5cm] and found out that there were no difference in survival and disease progression among then 0.1-1cm group and 1.1-5cm group and the survival was less when the residual tumor was more than 5cm [Winter E W *et al*, 2008]. Hence the cut off of 5cm was taken in our study.

Histomorphological changes have prognostic significance too. When the histomorphological changes observed among different study groups were analysed, hemosiderin-laden macrophages, psammoma bodies, foamy macrophages, and inflammatory cells were seen more in the post chemotherapy group according to Sassen S, *et al*'s study [Sassen S *et al*, 2007]. KhandakarB, *et al* in their study had assigned scores to the findings of post chemotherapy induced changes seen in ovary including fibrosis, calcification, cholesterol clefts, foamy and hemosiderin-laden macrophages, inflammatory cells, cytoplasmic degeneration, bizarre nuclei and anisonucleosis and had found that the median survival was longer when the score was more than ten [Khandakar B *et al*, 2015].

Samrao D, *et al* in their study had observed that stromal fibrosis seen post chemotherapy had a significant role in predicting the prognosis [Samrao D *et al*, 2012]. Severe fibrosis is associated with longer survival according to their study. When severe fibrosis is associated with more than fifty percentage necrosis then prognosis became better according to their study. Mc Cluggage WG, *et al* calculated the mean mitotic activity and the mean nuclear area in their study and found that the mitotic activity and the nuclear area were increased in the post chemotherapy ovarian tumors [McCluggage W G *et al*, 2002]. Fibrosis, inflammatory cells, fibrinous debris, psammoma bodies and cholesterol clefts were the chemotherapy induced changes observed in their study. This is consistent with our findings. McCluggage W G, *et al* in their study had also observed that psammoma bodies without tumor residue predict good tumor response [McCluggage W G *et al*, 2002].

Wang Y, *et al* in their study had observed dense fibrosis, chronic inflammatory infiltrate, and hemosiderin-laden macrophages, large amount of eosinophilic cytoplasm, vacuoles, hyperchromatic bizarre nuclei with coarse chromatin

clumping, prominent nucleoli and multinucleated tumor giant cells, which were also seen in our study[Wang Y *et al*, 2013]. Stromal fibrosis with hyalinisation, psammomatous calcification, inflammatory cells, foamy macrophages, bizarre nuclei and cytoplasmic degenerative changes were observed in the post chemotherapy samples in Khandakar B *et al*' study like our study [Khandakar B *et al*, 2014]. Moderate fibrosis, necrosis, residual tumour, extensive inflammation and psammoma bodies were observed as post chemotherapy changes in Tiwana KK, *et al*'s study as seen in our study [Tiwana K K *et al*, 2015]. Moderate fibrosis was more commonly observed in their study contrast to our study where mild fibrosis was observed.

Histological type and molecular studies also influence the prognosis. Tumors with BRCA mutation respond well to chemotherapy. Mucinous tumors respond less and endometrioid tumor responds better to the recent neo adjuvant chemotherapy [Marszalek A *et al*, 2010]. Immunohistochemical markers like Ki67, loss of E cadherin, Bcl2 negativity and ER status are inversely related to the patient's survival according to Khandakar B, *et al*'s study and Dian D, *et al*' study [Khandakar B *et al*, 2014, Dian D *et al*, 2011].

McCluggage W G, *et al* in their study had mentioned that omentum with stromal reactions were clues for omental involvement and it should more carefully analysed for tumor deposits. Cytological changes post chemotherapy could not be easily identified in the omental specimens. The foamy cytoplasm and small nuclear size could be mistaken for histiocytes and markers are needed in case of doubt [McCluggage W G *et al*, 2002].

Cytological changes that are observed post chemotherapy poses diagnostic challenges to the reporting pathologists. As the morphology is altered post chemotherapy and changes such as more cytoplasmic eosinophilia, bizarre nuclei, smudged chromatin, extensive necrosis and fibrosis are observed leading on to confusion in the categorization and grading of the tumor. Pathologists should be aware of all these morphological changes encountered in the post chemotherapy specimens. And through sampling of the specimens to identify the residual disease and immuno histochemistry in difficult cases are necessary.

CONCLUSION

Tumor grading and tumor morphology undergoes tremendous changes post chemotherapy. Most of the stage IV tumors are given chemotherapy without pre-treatment biopsy based on radiographic analysis or ascetic fluid analysis. Pre chemotherapy biopsy is necessary in the pathologists view point to analyse the tumor better and it also helps to assess the tumor response. Pre chemotherapy biopsy also avoids diagnostic confusion and a long array of investigations to arrive at the diagnosis. Some of the chemotherapy changes like fibrosis, necrosis and size of the residual tumor has prognostic significance and they should be included in reporting the post chemotherapy specimens.

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How to cite this article:

Shifa S Ibrahim., SivakamiSaravanan and Kamaleshwari Kesavaraj.2016, Chemotherapy Induced Changes In The ovarian Tumors –Histomorphology As A Diagnostic And As A Prognostic Tool . *Int J Recent Sci Res.* 7(1), pp. 8571-8577.

TSSN 0976-3031