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Original Research Article

# Histopathological prognostic factors in post NACT ovarian cancers: A retrospective study

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ABSTRACT

**Background:** Epithelial ovarian carcinoma is the most common type of all the ovarian cancers. The patients with advanced stage are initially treated with neo-adjuvant chemotherapy followed by interval debulking surgery. The high mortality rate is mainly due to advanced stage disease at initial presentation.
**Materials and Methods:** This a retrospective study carried out in department of pathology at Bhagwan Mahaveer cancer hospital, Jaipur. The retrospective cases data was collected and analyzed from patient records on basis of inclusion and exclusion criteria.
**Result**: Patients of advanced ovarian cancer with fibrosis grade 3, necrosis grade 2, presence of psammoma bodies, presence of collagen deposition, low Ki67 index, positive ER status were associated with longer DFS (p value= 0.014,0.029,0.033,0.028,0.001 and 0.001 respectively) and OS (P value 0.025,0.005,0.002,0.015,0.001 and 0.001 respectively).
**Conclusion:** We propose that the prognostic histopathological parameters analysed in our study in post NACT patients of ovarian carcinoma should be reported in final histopathological report, as these factors can provide an extra tool for clinicians to optimize patient management and care.



## 1. Introduction

Ovarian cancer is the second most common cause of cancer in women. It usually occurs in the sixth and seventh decades of life.[1–3] In patients with a positive family history the risk is between 10 to 40 per cent.[4] Epithelial ovarian cancer is the most common type of all ovarian cancers. They are aggressive tumors, which often present with advanced stage.[5–8] The patients with advanced stage are initially treated with neo-adjuvant chemotherapy followed by interval debulking surgery.[9] The high mortality rate is mainly due to advanced stage disease at initial presentation.[10]

There are various indicators to predict the response to treatment and prognosis of patients. However, despite parameters, it is important to document the chemotherapy induced histomorphological alterations in tumour as these might be helpful in prediction of tissue response to treatment.[11] There are very limited studies which evaluated the histomorphological factors for epithelial ovarian carcinoma and correlated with disease-free survival and overall survival. Therefore, this study was conducted with the aim of identification of histomorphological parameters such fibrosis, necrosis, inflammation, psammoma bodies, atypical mitosis, collagen deposition, Ki67 and ER status in post neoadjuvant chemotherapy patients of ovarian

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carcinoma.

## 2. Materials and Methods

The present study was a retrospective, observational, single Centre study conducted in department of pathology, BMCHRC, Jaipur. Treatment records of 150 patients of post NACT ovarian carcinoma who underwent interval cytoreduction with regular 3 year follow up were collected. Advanced Cases (Stage 3c and 4) of ovarian carcinoma including patients of all age groups who underwent optimal interval debulking surgery after 3or 4 or 6 cycles of paclitaxel and carboplatin regimen of neoadjuvant chemotherapy were included. Patients who lost to follow up and patients with diagnosis of Germ cell tumours, sex cord stromal tumors and other non-surface epithelial types were excluded. All details regarding extent of disease such as Omental deposits/caking, peritoneal nodules, Pelvic and para-aortic Lymph Node status, Ascitic Fluid were recorded as per clinical and radiological evidence in treatment records. The histopathological features such as Fibrosis which was scored as mild (grade 1), moderate (grade 2), and severe (grade 3), Necrosis scored as grade 0 if absent or minimal, grade 1+ if between 1% to 50% (1+), and grade 2 + when >50%, Inflammation scored as mild (grade 1) or extensive (grade 2) were recorded. Other features such as Presence or absence of Psammoma bodies, Lymphovascular invasion, perineural invasion, capsular invasion, collagen deposition was also recorded. Atypical mitosis was considered as frequent if mitotic activity was more than 12/ 10 hpf and infrequent if less than or equal to 12/ 10 hpf. The grading cutoffs were taken on basis of previous studies.[12]

Immunohistochemistry was applied for other two prognostic factors which are Ki 67 and Estrogen receptor status. Ki67 index was taken as low if <_ 20% and high if >20%. All data thus collected was entered in microsoft excel to prepare master chart and was subjected to statistical analysis. Linear variables were summarized as mean and standard deviation while nominal and categorical variables were expressed as proportions [%]. Chi –square test /fischer –exact test were used for nominal and categorical variables. P value < 0.05 was taken as significant. Statistical analysis was done using Chi square test and p value was calculated for Correlation of these histological prognostic factors with 3 year overall survival and disease-free survival.

## 3. Results and Discussion

In our study median age observed was 55 years. Samrao et al[12] in their study had median age as 57 years. Serous adenocarcinoma was found as the most common histological type in 94.67% patients followed by endometrioid carcinoma (4% patients) and mucinous adenocarcinoma (1.33% patients). Similarly, M. Muraji et al[13] in their study found serous adenocarcinoma as the most common histological type (70.2% patients) followed by endometrioid (3.2% patients) and mucinous adenocarcinoma type (1.6% patients).

**Table 1:** Patients characteristics

| Patients Characteristics | n (%) |
|---|---|
| **Age(Years)** | |
| 1. Median | 55.00 |
| 2. Range | 21-80 |
| **Histological Type** | |
| 1. Endometrioid | 6 (4%) |
| 2. Mucinous | 2 (1.33%) |
| 3. Serous | 142 (94.67%) |
| **Ascites** | 67 (44.7%) |
| **Cytology Positive of ascitic fluid** | 43 (64.2%) |
| **Extent of Disease** | |
| 1. Omental metastasis | 83 (55.3%) |
| 2. Peritoneal metastasis | 94 (62.7%) |
| 3. Lymph Node metastasis | 46 (30.7%) |
| **Capsular Invasion** | 85 (56.7%) |
| **Lymphovascular Invasion** | 20 (13.3%) |
| **Perineural Invasion** | 0 |
| **Recurrence** | 83 (55.3%) |
| 1. Distant Metastasis | 67 (80.7%) |
| 2. Local Recurrence | 16 (19.3%) |
| **Deaths** | 98 (65.3%) |
| **Fibrosis** | |
| 1. Grade 1 & 2 | 86 (57.3%) |
| 2. Grade 3 | 64 (42.7%) |
| **Necrosis** | |
| 1. Grade 0 & 1 | 129 (86%) |
| 2. Grade 2 | 21 (14%) |
| **Psammoma bodies** | |
| 1. Absent | 86 (57.3%) |
| 2. Present | 64 (42.7%) |
| **Inflammation** | |
| 1. Grade 1 | 77 (51.3%) |
| 2. Grade 2 | 73 (48.7%) |
| **Collagen Deposition** | |
| 1. Absent | 138 (92%) |
| 2. Present | 12 (8%) |
| **Atypical Mitosis** | |
| 1. Frequent | 114 (76%) |
| 2. Infrequent | 36 (24%) |
| **Ki 67** | |
| 1. High >20% | 44 (29.3%) |
| 2. Low (<20%) | 106 (70.7%) |
| **Estrogen Receptor status** | |
| 1. Absent | 53 (35.3%) |
| 2. Present | 97 (64.7%) |

The pretreatment serum CA125 levels below 500U/ml was observed in 33 patients (22%) and 117 patients (78%) had levels above 500U/ml. Whereas, Post NACT serum CA 125 levels below 35U/ml was observed in majority of the patients 68 (45.33%). In a study by Batra S et

**Table 2:** Correlation of histopathological factors with 3 year OS and DFS

| Histopathological parameter | Recurrence Patients (%) | p value | Deaths Patients (%) | p value |
|---|---|---|---|---|
| Fibrosis (Grade 1 & 2 Vs 3) | 55 (63.95%) vs 28 (43.75%) | 0.014 | 60 (69.77%) vs 38 (59.38%) | 0.025 |
| Necrosis(Grade 0 & 1 Vs 2) | 76 (58.91%) vs 7 (33.33%) | 0.029 | 90 (69.77%) vs 8 (38.10%) | 0.005 |
| Psammoma Bodies (Absent Vs Present) | 54 (62.79%) vs 29 (45.31%) | 0.033 | 65 (75.58%) vs 33 (51.56%) | 0.002 |
| Inflammation (Grade 1 Vs 2) | 44 (57.14%) vs 39 (53.42%) | 0.647 | 51 (62.23%) vs 47 (64.38%) | 0.812 |
| Collagen Deposition (Absent Vs Present) | 80 (57.97%) vs 3 (25%) | 0.028 | 94 (68.12%) vs 4 (33.33%) | 0.015 |
| Atypical Mitosis (Frequent Vs Infrequent) | 60 (52.63%) vs 23 (63.89%) | 0.236 | 71 (62.28%) vs 27 (75%) | 0.162 |
| Ki 67 (Low Vs High) | 45 (42.45%) vs 38 (86.36%) | 0.001 | 57 (53.77%) vs 41 (93.18%) | 0.001 |
| ER (Positive Vs Negative) | 44 (83.02%) vs 39 (40.21%) | 0.001 | 45 (84.91%) vs 53 (54.64%) | 0.001 |

al[14] it was observed that 74% patients had CA 125 levels >500U/ml followed by 26% with CA 125 levels < 500U/ml on initial presentation. After treatment, 44% patients had CA-125 values within the normal range (<35U/ml) while 46%. Ascites was present in 67 patients (44.7%), out of which cytology was positive for malignant cells in 43 patients (64.2%). Muraji et al[13] in their study observed ascitic fluid positivity in 66.1%. 83 patients (55.33%) showed omental metastasis, 94 patients (62.67%) showed peritoneal metastasis and lymph node metastasis was seen in 46 patients (30.67%). Naz et al[15] also observed omental metastasis in 51% patients in their study. Chen et al[7] observed peritoneal metastasis in 63.5% patients and lymph node metastasis in 30% patients in their study respectively.

Capsular invasion was seen in 56.7% patients, LVI was observed in 13.33% patients while PNI was not seen in any of the patient. The results were comparable to the study conducted by Naz et al[15] which showed capsular invasion in 61% patients and the incidence of LVI was 17.5% in study by Matsuo et al.[16]

Recurrence within 3 years was seen in 83 patients (55.33%), out of which local recurrence was seen in 16 patients (19.3%) and distant metastasis was seen in 67 patients (80.7%). Samrao et al[12] observed recurrence in 53.73% patients and Paik et al[17] observed local recurrence in 16.7% and distant metastasis in 83.3%. 98 patients died within 3 years follow up. Hence, the 3-year survival rate observed was 34.7%. Nandwani et al[9] observed 3 years overall survival as 34.8% in patient of Ovarian Carcinoma.

### *3.1. Prognostic histopathological factors*

In our study, patients with grade 1 and 2 fibrosis, recurrence was seen in 55 patients (63.95%) and 69.77% patients died within 3 years while patients with grade 3 fibrosis showed recurrence in 28 patients (43.75%) and 59.38% patients died within 3 years. In a study conducted by Samrao et al,[12] the patients with fibrosis grade 1 and 2, recurrence was seen in 36.7% patients and 40% patients died within 3 years, while patients with grade 3 fibrosis, recurrence was seen in only 18.7% patients and 25.3% patients died within 3 years. The correlation of fibrosis grade with recurrence and deaths within 3 years was significant statistically in our study as well as in study by Samrao et al.[12] (p-0.014, 0.025).

In patients with necrosis grade 0 and 1 necrosis, recurrence was seen in 76 patients (58.91%) and 90 (69.77%) patients died during 3 years follow up, while patients with grade 2 necrosis showed recurrence in 7 patients (33.33%) and 8 (38.10%) patients died during 3 years follow up. Samrao et al[12] in their study also found that patients with necrosis grade 0 and 1, recurrence was seen in 50.7% patients and 60% patients died within 3 years while patients with necrosis grade 2, only 4.7% patients had recurrence and 5.3% patients died within 3 years. The association of necrosis grade with recurrence and deaths was significant statistically in our study (p-0.029, 0.005) and in study by Samrao et al.

Similarly, T. Le et al[18] also demonstrated that the lack of or minimal tumor necrosis after neoadjuvant chemotherapy is independent and significant risk factor for recurrence in patients of ovarian carcinoma.

The patients with presence of psammoma bodies showed recurrence in 45.31% and 51.56% patients died within 3 years while in absence of psammoma bodies, recurrence was seen in 62.79% patients and 75.58% patients died within 3 years. This correlation of psammoma bodies with recurrence and deaths within 3 years was also significant. (p-0.033, 0.002). Motohara et al[19] in their study concluded that the presence of psammoma bodies is a favorable indicator in serous ovarian cancers which leads to better long-term survival.

Grade 1 inflammation was seen in 51.3% patients and 48.7% patients showed grade 2 inflammation. In patients with grade 1 and grade 2 inflammation, recurrence was seen

in 57.1% and 53.4% patients respectively whereas, 62.23% and 64.38% patients died in within 3 years with grade 1 and grade 2 inflammation respectively. This correlation of inflammation grade with both recurrence and death were insignificant statistically (p-0.647, 0.812). Samrao et al[12] in their study found mild (grade 1) inflammation in 53.73% patients and extensive inflammation in (grade 2) in 46.27% patients with non-significant association.

Collagen deposition was seen in 8% patients. In patients with presence of collagen, recurrence was seen in 25% patients and 33.33% patients died within 3 years and in patients with no collagen deposition, recurrence was seen in 57.97% and 68.12% patients died within 3 years. This correlation of collagen deposition bodies with recurrence and deaths within 3 years was also significant. (p 0.028, 0.015). There is no published literature regarding study of collagen deposition in ovarian carcinoma. However, collagen deposition was found to be significantly correlated to pathologic response and tumor regression grade in breast carcinoma patients in a study by Sethi et al.[20]

Atypical mitosis was frequent in 76% patients while infrequent in 24% patients. Patients with frequent atypical mitosis showed recurrence in 52.63% patients and 62.28% patients died within 3 years. The correlation of atypical mitosis with either recurrence or deaths was insignificant statistically (p-0.236, 0.162). Mitotic counts were not employed for the distinction of low-grade from high-grade serous carcinoma. Rather, low-grade serous carcinoma was considered as having only infrequent mitotic figures while high-grade serous carcinoma has readily identifiable mitotic activity.

IHC staining for low Ki 67 index (<20%) was observed in 70.67% patients out of which recurrence was seen in 42.45% and 53.77% died within 3 years and high Ki 67 was observed in 29.33% patients which showed recurrence in 86.36% and 93.18% died within 3 years. The correlation of Ki 67 with recurrence and deaths was significant. (p-0.001, 0.001). Polcher et al[21] in their study observed 70% patients with low Ki67 index and 30% with high Ki67 index and concluded that high Ki-67 nuclear staining is associated with a greater risk of tumor recurrence and unfavorable survival rates in ovarian cancer patients. Estrogen receptor status was observed positive in 97 cases (64.67%) which showed recurrence in 40.21% patients and 54.64% patients died within 3 years and 53 (35.33%) patients were negative for ER status and showed recurrence in 83% patients and 84.9% patients died within 3 years. ER status was significant prognostic factor in our study (p- 0.001, 0.001). Hogdall et al[22] in their study showed the significant correlation of ER expression with improved patient survival.

## 4. Conclusion

There are limited studies in literature available on neoadjuvant chemotherapy induced histopathological changes of ovarian cancer. So, we stress upon the fact that there is need to change reporting formats of ovarian carcinoma incorporating fibrosis grade, necrosis grade, inflammation grade, psammoma bodies, collagen deposition, atypical mitosis, Ki 67, ER receptor positivity as histopathological changes so that they can provide an extra tool to optimize patient management and care.

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None.

## 6. Conflict of Interest

None.

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