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Original Article

Data Analysis of Ovarian Cancer Patients for Feasibility of Treatment in a Radiation Oncology Department

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Abstract

Introduction: Ovarian cancer is not only the most common but also the most lethal gynecological malignancy, partly, because the majority of patients present with advanced disease. However, as is true for so many cancers, the management of patients with ovarian neoplasms has changed substantially, and outcome results have improved considerably over the years.The reasons for this are many. For example, major advances in chemotherapy have resulted in improved survival, and the role of surgery is constantly evolving and being refined.

Purpose: A retrospective data analyses of ovarian cancer patients to observe their contemporary management in a radiation oncology departmental set up and the post-treatment outcome of these patients.

Materials and Methods: The case records of 117 ovarian neoplasm patients registered in our department from 2011 to 2018 were analyzed. The clinical, histopathological, and treatment details were noted. Contemporary treatment protocols were used.

Results: Of the 117 patients of ovarian cancer treated in our department with conventional diagnostic, imaging, surgical, and contemporary chemotherapy protocols, we found management of such patients is possible with optimum outcomes.

Conclusion: Ovarian cancer patients can safely and optimally be treated in a radiation oncology department.

Key words: Clinicopathologic profile, Ovarian cancer, Treatment in radiation oncology department

INTRODUCTION

Primary carcinoma of the ovary is the fourth most common cancer among women in developed countries. It is the leading cause of death among all gynecologic cancers. Worldwide ovarian cancer incidence rates vary widely between different geographic regions and ethnic groups with the highest incidence in Northern Europe, and lowest incidence is in Japan.[1] Ovarian cancer is not a single entity but represents tumors of epithelial, germ cell, and sex cord-stromal origin. Approximately 90% of ovarian cancer is epithelial in origin presenting in advanced stages in most of the patients, while other types of ovarian cancer such as germ cell and sex cord-stromal tumors are often localized in distribution with a more favorable prognosis. While epithelial tumors are seen in elderly women, germ cell tumors occur in young women and sex cord-stromal tumors occur in young as well as elderly women.[2]

According to the International Federation of Gynecology and Obstetrics (FIGO), patients with ovarian cancer have to be staged surgically which is important for planning therapy and assessing prognosis with the goal being to remove as much disease as possible. The key elements of surgical staging for ovarian cancer are the same for all types of tumors except in young patients wishing to preserve fertility.[1]

Ovarian cancer is a very chemosensitive disease,[1] but still, most patients relapse sooner or later needing further treatment with only a handful of patients achieving a long-term survival and a 5 year survival in Stage III/IV epithelial ovarian cancer patients as low as 12% over the past 30 years.[3,4]

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The purpose of this study was to evaluate and review the clinicopathological profile and feasibility of the management of ovarian cancer patients in radiation oncology department.

MATERIALS AND METHODS

Case records of 117 patients with a diagnosis of ovarian cancer registered in our department from 2011 to 2018 (both years included) were taken for the review (in addition to these, four patients were registered in our department during this period who had only imaging evidence of ovarian malignancy but did not follow so were excluded from the study). Details included registration number (RT number), age, clinical presentation, performance status, type of imaging, histopathological type, treatment given, and post-treatment outcome.

RESULTS

A total of 117 patients with histologically documented ovarian tumors were enrolled over a period of 8 years from 2011 to 2018. For these patients, the imaging modality used for diagnosis was contrast-enhanced computerized tomography (CECT) abdomen and pelvis, an ultrasonography (USG) abdomen and pelvis, magnetic resonance imaging pelvis, and transvaginal sonography. Of all these, CECT was the most commonly used imaging modality followed by USG. Based on the imaging findings regarding the extent of disease, patients were subjected to various types of procedures to obtain a histopathological diagnosis, for example, classic surgical staging procedure for ovarian cancer (total abdominal hysterectomy + bilateral salpingo-oophorectomy [TAH + BSO]), diagnosis based on ascitic fluid cytology, laparoscopic biopsy, USG guided fine-needle aspiration cytology/core needle biopsy, and exploratory laparotomy. On histopathological analysis, 93 patients had epithelial tumors, 11 patients had germ cell tumors, and 13 had granulosa cell tumors [Table 1].

Within the epithelial tumors, the malignant serous tumor was the most common (46 patients) followed by malignant mucinous tumor (39 patients). In addition to these two main histologic types, other types were also seen, for example, primary peritoneal serous carcinoma, clear cell tumor, small cell carcinoma, and malignant endometrioid tumor. Staging wise distribution of epithelial tumors is shown in Table 2. Eight patients had Stage IV disease. The age range for epithelial origin tumors was between 18 and 74 years.

Among the 11 germ cell tumors, the maximum number of patients had mature cystic teratomas followed by dysgerminoma, in addition to mixed germ cell tumor and yolk sac tumor (endodermal sinus). All these patients were Stage I with an age range between 15 and 24 years.Among the 13 patients of granulosa cell tumor, all had Stage I disease, with an age range between 18 and 65 years.

Treatment

Epithelial tumors

Out of a total of 93 patients with epithelial tumors, 42 patients received chemotherapy in the neoadjuvant setting in view of an advanced stage of disease and remaining 51 patients received chemotherapy in the adjuvant setting (post-surgery).

Table 1: Patient characteristics (*n*=117)

Imaging modality	CECT 82	USG 23	MRI 10	TVS 2		
Histopathological diagnosis established by	TAH+BSO 52	Ascitic fluid cytology 9	Laparoscopic biopsy 10	Image-guided biopsy 17	Exploratory Laparotomy 28	Left supraclavicular node biopsy 1
Histopathology	Epithelial 93 Serous 46 Mucinous 39 Clear cell 2 Endometrioid 1 PPSC 4 Small cell 1	Germ cell 11 Mixed 2 Dysgerminoma 3 Yolk sac 2 Mature teratoma 4	Sex cord-stromal 13 Granulosa cell tumor 13			
Stage (FIGO)	IA 10 IC 12 IIA 9 IIB 4 IIC 2 IIIB 14 IIIC 34 IV 8	I in 11	IA 8 IC 5			
Age range (years)	18–74	15–24	18–65			

FIGO: International Federation of Gynecology and Obstetrics, TAH+BSO: Total abdominal hysterectomy+bilateral salpingo-oophorectomy, CECT: Contrast-enhanced computerized tomography, USG: Ultrasonography, MRI: Magnetic resonance imaging, TVS: Transvaginal sonography, PPSC: Primary peritoneal serous carcinoma

Neoadjuvant

Forty-two patients were treated with neoadjuvant (upfront) chemotherapy after diagnosis. In view of the advanced clinical stage, these patients were not operated, but a histopathological diagnosis was established by either a laparoscopic biopsy, imaging-guided biopsy, laparotomy with biopsy from accessible mass, ascitic fluid cytology, and biopsy from the left supraclavicular lymph node [Table 2].

Histopathology wise the most common type was serous (23 patients) followed by mucinous (15 patients). Eight patients had Stage IV disease (four had pleural effusion, one had metastasis left supraclavicular lymph node, and three had liver metastasis), while 34 patients had Stage III disease. For these 34 patients achieving an optimum, surgical resection was not possible, in view of grossly palpable disease and most cases, associated with ascites, hence they were given upfront chemotherapy. The chemotherapeutic drugs used were paclitaxel and carboplatin intravenously repeated at 3 weekly intervals for three cycles.

After three cycles of neoadjuvant chemotherapy, 12 patients showed response, including two Stage IV patients with the downsizing of the disease and an interval cytoreduction was possible. While in rest 30 patients, chemotherapy was continued because response assessment at the completion of three cycles showed persistent disease. At the end of six cycles of chemotherapy, 23 patients showed a response and were therefore referred for surgical cytoreduction, but seven patients totally failed to respond to first-line chemotherapy. These were offered second-line chemotherapy [Table 3].

Table 2: Treatment given to epithelial tumors (*n*=93)

Surgery	Adjuvant chemo 47	Neoadjuvant chemo 42
TAH+BSO	49	
Laparotomy with ipsilateral salpingo-oophorectomy	1	
Laparotomy with BSO	1	
Laparoscopic biopsy		10
Imaging guided biopsy		17
Laparotomy with biopsy/ mass excision		5
Ascitic fluid cytology		9
Left supraclavicular node		1

TAH+BSO: Total abdominal hysterectomy+bilateral salpingo-oophorectomy

Table 3: Profile of response achieved after neoadjuvant chemotherapy

Neoadjuvant chemotherapy	Response after three cycles	Response after six cycles	Failed to chemotherapy
42 patients	12 patients	23	7

For the 35 patients who returned after surgical cytoreduction (12 patients after three cycles and 23 patients after six cycles of neoadjuvant chemotherapy), all were given three additional cycles of post-operative systemic chemotherapy with the same drugs and schedule as before. Out of these, 23 patients are disease free, alive and on follow-up which included one patient who relapsed after 8 months (platinum-sensitive disease) and received chemotherapy again, while 12 patients relapsed at different times after first-line chemotherapy and received further lines of chemotherapy but ultimately died.

Adjuvant

Out of a total of 51 patients who presented to our department with upfront surgery, in 49 patients diagnosis and staging were established by TAH + BSO, while laparotomy with ipsilateral salpingo-oophorectomy and laparotomy with BSO were done in one patient each [Table 2].

Histopathologically serous type was more common than mucinous, 29 patients versus 22 patients. Stage wise most patients had Stage IIIB disease followed by Stage IC [Table 4].

Of the ten patients with Stage IA disease, four patients had either a Grade I or II disease and hence were put on close follow-up alone while rest of the 47 patients out of a total of 51 were treated with first-line systemic chemotherapy, same drugs and schedule as above for six cycles with interval assessment. All the patients started on chemotherapy received full six cycles of chemotherapy with paclitaxel and carboplatin. After finishing chemotherapy, the patients were put on regular follow-up with assessment based on tumor markers and imaging as and when needed. Out of these 47 patients who received systemic chemotherapy, 33 patients are disease-free, alive, and on follow-up to date while 14 patients have failed treatment at different times during follow-up including two patients who had initially Stage I disease and were put on close observation alone. Failing patients received subsequent lines of chemotherapy depending on their sensitivity to platinum agents, but ultimately all these relapsing patients succumbed to their disease at different times.

Table 4: Profile of patients who received adjuvant chemotherapy

Histopathology		Stage	Chemotherapy given	No chemotherapy
Serous 29	Mucinous 22	IA=10 IC=12 IIA=9 IIB=4 IIC=2 IIIB=14	47	4

Germ cell tumors

All the 11 patients were first subjected to surgery. The type of surgery done, the histopathological type of tumor, and the chemotherapy given to patients is shown in Table 5. All the patients with mixed germ cell tumors, dysgerminoma, and yolk sac tumors received chemotherapy in the form of bleomycin, etoposide and cisplatin intravenously at 3 weekly intervals for four cycles. All of these patients are alive and on follow-up. Four patients of mature cystic teratoma who did not receive chemotherapy are on close follow-up alone.

Granulosa cell tumors

In all 13 patients, surgery had been done before patients were referred to our department. The details about the type of surgery done, histopathology types and further follow-up are shown in Table 6. After surgery, all these are on follow-up alone with monitoring by tumor markers.

DISCUSSION

The aim of this study was to analyze the feasibility of treating ovarian cancer patients in a radiation oncology departmental set up. Because our department is actually a radiation oncology cancer department (being more involved with hi-tech equipment and gadgets) we were interested to actually observe whether ovarian cancer patients could be optimally treated in our departmental set up with the same protocols and the same level of care that such patients receive when they are treated in a more conventional medical oncology departmental set ups, especially since these patients develop frequent and multiple relapses and hence require multiple lines of chemotherapeutic drugs.

Table 5: Treatment and histopathology of germ cell tumors (*n*=11)

Surgery		HP	Adjuvant chemo	Outcome
Left oophorectomy	02	Mixed GCT	BEP	On follow-up
Left salpingo-oophorectomy	03	Dysgerminoma	BEP	On follow-up
	02	Yolk sac tumor	BEP	
B/L cyst excision	01	Mature cystic teratomas	Close surveillance	On follow-up
Left oophorectomy	03	Mature cystic teratomas	Close surveillance	On follow-up

GCT: Germ cell tumor, BEP: Bleomycin, etoposide, and cisplatin

Table 6: Treatment given to granulosa cell tumors (*n*=13)

Surgery		Histopathology	Outcome
Right oophorectomy	04	Granulosa cell tumor	On close surveillance
Left salpingo-oophorectomy with right ovarian biopsy	02	Granulosa cell tumor	On close surveillance
Left oophorectomy	02	Granulosa cell tumor	On close surveillance
BSO with the disease in left ovary and cystic lesion in right ovary	03	Granulosa cell tumor	On close surveillance
TAH+BSO with the disease in right ovary	02	Granulosa cell tumor	On close surveillance

TAH+BSO: Total abdominal hysterectomy+bilateral salpingo-oophorectomy

Ovarian neoplasms are common. Of genital tumors in women, ovarian cancer accounts for a third, about the same proportion as carcinoma of endometrium and cervix.[3] Ovarian cancer is predominantly a disease of the elderly.[2] In our department, we come across ovarian cancer patients more frequently than either endometrial or cervical cancers, perhaps due to progressive affluence seen in our society and a possible low cervical cancer incidence due to social and religious practices being practiced here.

Approximately 80% of women with ovarian cancer have a FIGO Stage III/IV at initial presentation and survival is consequently poor (overall 5-year survival of 30–40%); hence, the disease is frequently called the "silent killer."[1] More specifically, elderly patients with ovarian cancer have poorer survival, undergo proportionally fewer surgical procedures, receive less aggressive treatments, and are less likely to be referred to a gynecologic oncology specialist. In our study, also, we found a predominance of elderly patients with epithelial origin tumors and a comparatively younger age group with germ cell and granulosa cell tumors. The outcome benefit of achieving no gross residual disease following surgical cytoreduction may be lost on those elderly patients who tolerate the surgery poorly-emphasizing the need for validated pre-operative assessments to help guide appropriate patients to surgery and avoid unnecessary complications for those who should have an alternative treatment.[2] Therefore, a proper selection of patients for upfront surgery should be done to keep surgical mortality as low as possible.

The histopathological classification of malignant ovarian tumors accepted by the World Health Organization and the FIGO divides them into four major types;

1. Epithelial tumors
2. Sex cord-stromal tumors
3. Germ cell tumors
4. Miscellaneous tumors, for example, Wilms' tumor, lymphoma, and small cell tumor.

While epithelial tumors make 90% of ovarian cancer, germ cell tumors constitute around 2–3%, sex cord-stromal tumors around 5%, and miscellaneous around 1–2%. The standard surgical staging procedure for all ovarian neoplasms,

except in young patients wishing to preserve fertility in whom staging is performed without removing contralateral ovary and tube and without hysterectomy, if the extent of disease allows to do so, is TAH + BSO.[1] This histologically confirms the diagnosis, removes a major portion of disease, and helps in planning therapy and assessing prognosis. The main goal of the procedure is to estimate the extent of the disease while, ideally, achieving macroscopic clearance with a so-called maximal or optimal debulking procedure (≤1 cm diameter residual tumor).[2] However, epithelial tumors usually are seen in elderly postmenopausal women and present in advanced stages, posing significant therapeutic challenges. Hence, in such patients alternative upfront treatment options such as intravenous chemotherapy rather than surgery may be considered, followed by interval cytoreduction. Theoretical advantages of neoadjuvant chemotherapy in this setting are a more rapid improvement in quality of life, and, if interval debulking surgery is ultimately performed, a technically more feasible operation with shorter hospitalization and less morbidity.[2] In our study, we found use of neoadjuvant (upfront) systemic chemotherapy quite frequently especially for all Stage IV and Stage IIIC patients. In fact, our aim was to keep a very low threshold for upfront systemic chemotherapy while treating advanced epithelial ovarian cancer patients because it is our experience that an incompletely or inadequately performed surgical debulking does not help the cause but lands the patient in a situation where subsequent chemotherapy is not effective and rather poorly tolerated.

Although numerous combination chemotherapy regimens have been studied over the past few decades, the combination of platinum and a taxane compound such as paclitaxel is now the standard first-line in post-operative as well as in neoadjuvant setting with response rates of 70% for patients with sub optimally debulked disease and over 80% for patients who are optimally cytoreduced.[5,6] A total of six cycles of such combination chemotherapy are considered a reasonable approach for the treatment of ovarian cancer patients when they require such treatments.[2] For the patients in our study, we followed the commonly accepted approach of using combination of paclitaxel and carboplatin intravenously for three cycles in neoadjuvant setting followed by interval cytoreduction if feasible, or to continue chemo for three more cycles in patients who achieve less than optimum response after three cycles. Patients who did not show any response or who did not become eligible for an optimal debulking after six cycles were offered palliative second and further lines of chemotherapy and supportive measures.

Germ cell tumors occur in younger women, while sex cord-stromal tumors are seen in young as well as elderly. Both these histopathological types are often localized in distribution, more amenable to surgical resection, and have a more favorable prognosis.[2] Hence, in most cases an upfront surgery are done followed by a reassessment regarding any further adjuvant treatment. In the M.D. Anderson series four, all patients who received post-operative bleomycin, etoposide, and cisplatin chemotherapy remained disease free and hence, this regime remains the preferred regimen for patients with germ cell tumors.[7] In our study, patients having mixed germ cell tumors, dysgerminoma, and yolk sac tumors were treated with same systemic chemotherapy after surgical resection (in most cases a fertility-preserving) had been done. Resection of mature teratomas has been shown to result in prolonged survival with little chance of recurrence two; hence, patients with mature teratoma histopathology in keeping with their benign nature and low chances of post-operative recurrences were subjected to close follow-up alone.

Ovarian sex cord-stromal (granulosa cell type) tumors often present with Stage I disease which has excellent prognosis, a 85% 10-year survival for this stage, and no need for post-operative adjuvant chemotherapy.[8] In our study, all granulosa cell tumor patients had Stage I disease and hence no post-surgery chemotherapy was administered.

Ovarian cancer is a very chemosensitive disease with a number of classes of drugs showing activity.[1]

Even though there have been major advances in the treatment of ovarian cancer with improvement insurvival, still most patients relapse and require further treatment, and only a minority with advanced disease achieve long-term survival. The results of the International Collaborative Ovarian Neoplasm Trial 1 and Adjuvant Chemotherapy in Ovarian Neoplasm Trial suggest that adjuvant chemotherapy can improve both progression-free and overall survival in patients with high risk, early stage ovarian cancer.[2] The time tested first-line chemotherapy drugs consisting of a taxane such as paclitaxel and a platinum agent such as carboplatin two were used in our study though very late, around one and a ½ year back, we have started the use of vascular endothelial growth factor receptor blocker like bevacizumab in recurrent disease settings, especially since its cost was slashed and people could afford to buy it. Most patients respond to the combination of these drugs, but true to its nature, ovarian cancer especially epithelial type shows quite high rates of relapse, which mandates a change in the subsequent drugs being used based on the sensitivity profile of these tumors.

CONCLUSION

Our experience of managing and treating ovarian cancer patients in our department was very reassuring and

encouraging keeping in mind our more time-consuming work on radiotherapy equipment involving patient planning and monitoring the treatment protocols. Hence, it would be concluded that ovarian cancer patients can safely be treated in a radiation oncology department provided all contemporary treatment protocols are applied.

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