

Cytoreductive Surgery for Advanced Epithelial Tumors of the Ovary: Technical Considerations and Outcome

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ABSTRACT

Purpose: To study the role of cytoreductive surgery in the management of advanced epithelial tumors of the ovary and its effect on survival.

Patients and Methods: A prospective study of fifty eight female patients presenting with stage III and VI epithelial ovarian tumors attending the National Cancer Institute, Cairo University during the period from January 2003 to of December 2004. All patients were evaluated clinically, radiologically (including plain chest-X-ray and abdomino-pelvic ultrasound and/or CT), laboratory work up and CA-125. Abdominal exploration under general anesthesia with intent of maximum surgical cytoreduction was performed for all patients. Patients were followed up during the period of the study by history and physical examination, CA-125 measurement and abdomino-pelvic ultrasound or CT.

Results: Our study included 58 female patients with advanced epithelial tumors of the ovary. Their age ranged from 18 to 73 years with a mean age of 49 years. Pathological distribution of the lesions were borderline malignancy in 5 patients (8.6%) and malignant in 53 patients (91.4%). According to FIGO classification there were 46 patients stage III (79%) and 12 patients stage VI disease (21%). Eighteen patients (31%) had surgery prior to admission to NCI. Cytoreductive surgery was done for 51 patients (88%), while 7 patients (12%) had exploration and biopsy only, one of whom had palliative colostomy for large bowel obstruction. Intraoperative surgical complications were encountered in 5 patients (8.6%), all were managed intraoperatively. We had no early postoperative mortalities and 8 postoperative morbidities (13.7%). All patients were referred for chemotherapy. Thirteen patients (22.4%) had local recurrence within the follow up period of the study which was between 8-24 months. One patient died from locally advanced disease and the rest of the patients were explored and lesions were surgically resected.

Conclusion: Surgery remains a major line of therapy in ovarian cancer including advanced lesions. Extensive procedures to maintain a R0 result are crucial to reach a satisfactory local disease control. The NCI, as well as all tertiary cancer centers, has an important role in providing this quality of surgery especially in advanced cases.

Chemotherapy remains the hope to ameliorate the survival especially in advanced cases. The close coordination between surgery and chemotherapy in the form of Intra-Peritoneal Hyperthermic Chemotherapy (IPHC) represents a hope for patients with advanced disease and should be introduced and established in all major cancer centers.

Key Words: Ovarian masses - Ovarian tumors - Surgical cytoreduction.

INTRODUCTION

Ovarian tumors are ranked as the 5th most common cancer in women. They account for 4% of all malignancies affecting females. They also constitute 40% of all gynecological malignancies. It is the main cause of death in all gynecological tumors and it is the 5th leading cause of death in females in general. Women are at risk of developing ovarian cancer during their life time in 1.5% of them [1].

There are different pathological types of ovarian tumors according to cell of origin, but epithelial tumors are the most common type as they account for 80-90% of ovarian tumors. The grade of the tumor varies between borderline or low malignant potential to tumors of high grade or undifferentiated tumors [1].

Despite the fact that ovarian malignancy is usually diagnosed at an advanced stage, dissemination is often confined to the peritoneal cavity and spread outside the abdomen is a rare and late event. This makes from aggressive therapy directed at the peritoneal cavity an attractive option [2].

Diagnosis of ovarian tumors depends mainly on the clinical presentation of the patient, laboratory investigations and imaging modalities.

Patients may present without any symptoms during routine check up or with symptoms which include abdominal mass or distention, pelvic pain, gastrointestinal dysfunction and urinary frequency. The tumor marker CA-125 is considered an important factor in the diagnosis of ovarian tumors and as an indicator for local recurrence during the follow up period. CA-125 is elevated above 65 IU/ml in 85% of ovarian cancer cases at different stages and in 50% in stage I disease, 71% in stage II, 95% in stage III and up to 100% in stage VI [3]. Imaging modalities used in the diagnosis of ovarian tumors include, ultrasonography either abdominopelvic or transvaginal, as well as computed tomography (CT) scan. CT scan is accurate in 60% of cases. Magnetic resonance imaging (MRI) is used in selected cases. Aspiration biopsy cytology (ABC) is used in advanced cases especially if preoperative chemotherapy is to be given [4].

Diagnostic laparoscopy is considered a part of the diagnostic tools in ovarian tumors as a minimally invasive technique especially in patients with unexplained pain and small adnexal masses. It is helpful in staging of the disease and in procedures like ovarian cystectomy/oophorectomy [5].

Basic surgical procedures used in the management of advanced ovarian tumors include: primary cytoreduction, secondary cytoreduction, exploration with biopsy, interval cytoreduction, second-look laparotomy and laparoscopy. The role of cytoreduction in ovarian cancer has been investigated for more than 50 years and is now considered the standard approach in the primary surgical treatment, which is usually followed by chemotherapy as the majority of ovarian cancers are chemosensitive [6].

Cytoreductive surgery is a radical debulking operation designed to remove as much of the tumor load as possible so that subsequent adjuvant therapy can be given effectively and with curative intent. Cytoreduction includes total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy, supra or infra colic omentectomy, removal of peritoneal masses and involved structures. Cytoreduction is classified as R0, R1 or R2 depending on the completeness of the procedure. R0 was defined as complete tumor resection, R1 as tumor resection with left residual less than 2cm and R2 as tumor resection with residual equal to or more than 2cm [7].

Prognosis of ovarian cancer depends mainly on the stage of the disease. The 5 year survival in different stages is 70% for stage I; 50% for stage II; 15% for stage III and 10% for stage IV. The tumor class is either low malignant potential (LMP) where 5 year survival approaches 90-100%, or malignant with 5 year survival between 90-5% [8]. A worse prognosis is associated with some tumor histological types like choriocarcinoma and clear cell carcinoma, high grade tumors, increased aneuploidy and with oncogene expression: Ras, c-erb-B-2 and myc [9].

The aim of this work was to study the role of cytoreductive surgery in the management of stages III and VI epithelial tumors of the ovary as regards the surgical procedures, intraoperative and postoperative complications, and with follow up during the period of study which ranged from 8 to 24 months.

PATIENTS AND METHODS

This is a prospective study of 58 female patients attending the National Cancer Institute, Cairo University, during the period from January 2003 to December 2004 with advanced ovarian masses staged as stage III and VI according to FIGO classification and proved to be of epithelial origin after histopathological examination. All patients were evaluated clinically by complete history and physical examination, radiologically (including chest X-ray, abdominal, pelvic ultrasound and/or CT scan) and laboratory work up which included routine preoperative tests and the tumor marker (CA-125).

Exclusion criteria included stage I and II, surgically unfit patients due to medical causes and tumors other than epithelial origin. Abdominal exploration under general anesthesia with the intent of maximum surgical cytoreduction was performed for all patients, and the following surgical principles were advocated in all cases:

A vertical incision was usually used for proper exploration and to allow extension of the incision if needed. On entering the abdomen, aspiration of ascites or peritoneal lavage was performed for cytologic examinations then systematic evaluation of the abdominal cavity was performed starting by visualizing all peritoneal surfaces, including peritoneal surface of the anterior abdominal wall, omentum, small and large bowel, paracolic gutters, pelvis, mesenteric

and para-aortic areas and lower surface of the diaphragm, then palpation of intra-abdominal organs for any abnormality, then local assessment of the primary lesion and its relation to surrounding organs and structures for possibility of spread or invasion was performed.

Specimens were taken from the pelvis, right and left paracolic gutters and the under surfaces of the right and left hemi-diaphragms. Any encapsulated mass was removed intact if possible. Adhesions were noted and marked. All intestinal surfaces were evaluated and any suspicious areas were biopsied. Omentectomy and random peritoneal biopsies were performed. Aortic lymph node sampling was performed by stripping the nodal tissue from the vena cava and the aorta to the level of the left renal hilum. Pelvic lymph nodes were sampled. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. Every attempt was made to achieve maximal cytoreduction in appropriate circumstances leaving residual lesions less than 2cm size. Non radical procedures were performed in a small number of young patients refusing radical surgery.

Patients were Referred for Chemotherapy After Surgery. Three Chemotherapeutic Protocols were used:

- 1- Paclitaxel + Carboplatin.
- 2- Endoxan + Cisplatin.
- 3- Platinol + Vipid + Bleomycin.
- 4- Platinol + Holoxan + Bleomycin.

None of our patients received radiation therapy. Patients were followed up every month for the first 6 months then every 3 months thereafter. Follow up included complete physical examination, CA-125 measurement and abdomino-pelvic ultrasound or CT.

RESULTS

Our study included 58 female patients attending at the National Cancer Institute, Cairo University, during the period from January 2003 to December 2004 with advanced ovarian malignancy staged as stage III and VI. The ages of the patients ranged from 18 to 73 years with a mean age of 49 years. The disease distribution among each age group is shown in (Fig.1). There were 7 single (12%) and 51 married patients (88%). Among married patients, six

patients (10.3%) had no children, seven patients (12.1%) had one child, 10 patients (17.2%) had two children, 8 patients (13.8%) had three children, 6 patients (10.3%) had four children, 5 patients (8.6%) had five children, 7 patients (12.1%) had six children and two patients (3.4%) had seven and nine children, respectively (parity shown in Fig. 2). The pathological distribution of patients included borderline malignancy in 5 patients (8.6%) and malignant in 53 patients (91.4%) (Table1). According to FIGO classification, there were 46 patients (79.3%) stage III and 12 patients (20.7%) stage VI disease (Table 2). Eighteen patients had surgery prior to NCI admission, only three patients were considered to have adequate surgery while the rest of cases were re-explored.

All our patients were explored with the intent to do maximal cytoreduction. The types of surgery done are listed in (Table 3). Cytoreductive surgery was performed in 43 cases (74.9%), 19 patients (32.7%) had complete resection (R0) (Fig. 3), 17 patients (29.3%) had (R1) type of resection (Figs. 4-6) and 15 patients (25.8%) had (R2) type of resection (Figs. 7,8). Eight young patients with stage III disease (13.7%) had non radical procedures because they refused extensive surgery, while 7 cases (12%) had exploration and biopsy only without resection, 5 of them had interval debulking after chemotherapy (Table 4).

Intraoperative complications were encountered in 5 patients (8.6%). There was one urinary bladder injury due to extensive adhesions, two colonic injuries because of colonic involvement and two vascular injuries (one was inferior vena cava and the other was internal iliac vein), all were managed intraoperatively. There were no early postoperative mortalities. Blood transfusion was needed in 9 patients (15.5%), the transfused volume was 500ml in 8 cases and 1000ml in one case.

Post-operative surgical complications occurred in 8 patients (13.7%) as shown in (Table 5). Hospital stay ranged from 3 to 27 days, average 7.78 days. ICU admission was needed for one patient and she stayed for 16 days for cardiac problems.

All patients were referred for chemotherapy and referred back after completing full courses (usually 6 courses).

Recurrence post complete remission within the study period occurred in 13/58 patients (22.4%). The average duration to recurrence since the first line of treatment was 280 days. All recurrences occurred in patients with R1 and R2 resections. The site of recurrence was

in the pelvis in 7 cases, on the bowel in 3 cases and in different areas of peritoneum in 3 cases.

Total deaths during the study period was one patient 1/58 (1, 72%) from locally advanced disease.

Table (1): Pathological categories.

Pathological Categories	Patient No.	%
Borderline Malignant	5	8.6%
Malignant:	53	91.4%
Primary	51	88%
Second Primary*	2	3.4%
Total	58	100.0%

*Second primary in two patients who had breast cancer before.

Table (3): Surgical procedures done for 58 patients.

Procedures	Patient No.	%
Non-Radical Procedures:	15	25.8%
• Exploration ± Biopsy	7	12%
• Ovariectomy	5	8.6%
• USO	2	3.4%
• SAH-USO/BSO	1	1.7%
Radical Procedures:	43	74.2%
• (Completion) TAH-BSO	2	3.4%
• TAH-BSO + Omentectomy	20	34%
• Completion to TAH-BSO + Omentectomy	3	5.1%
• TAH-BSO + Omentectomy +LN Sampling/LND	4	6.8%
• TAH-BSO + Omentectomy +Peritonectomy	2	3.4%
• TAH-BSO + Omentectomy +Gut WLE	7	12%
• TAH-BSO + Omentectomy +Other WLE	1	1.7%
• Unclassified Debulking	4	6.8%
Total	58	100.0%

USO = Unilateral salpingo-oophorectomy.
BSO = Bilateral salpingo-oophorectomy.
SAH = subtotal abdominal hysterectomy.
TAH = Total abdominal hysterectomy.
LN = Lymph node.
LND = Lymph node dissection.
WLE = Wide local excision.

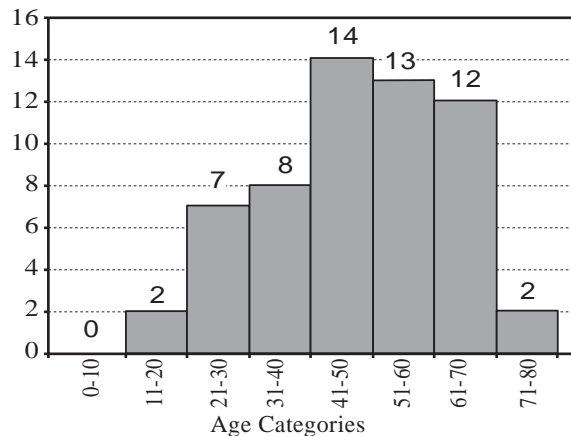


Fig. (1): Patients' age distribution.

Table (2): Patients' FIGO stagings.

FIGO staging	Patient No.	%
• III	46	79.3%
• IIIA	3	5.2%
• IIIB	1	1.7%
• IIIC	42	72.4%
• IV	12	20.7%
Total	58	100.0%

Table (4): NCI's surgical procedures categories.

Resection Category	Patient No.	%
• Debulking R0	19	32.7%
• Debulking R1	17	29.3%
• Debulking R2	15	25.8%
• Exploration/Biopsy	6	10.3%
• Palliative	1	1.7%
Total	58	100.0%

R0 = No residual, R1 = Residual <1ccm.
R2 = Residual >1ccm.

Table (5): Post operative complications.

Complications	Patient No.	%
Morbidity:	8	13.7%
• Wound Sepsis	1	1.7%
• Wound Dehiscence	1	1.7%
• Hemorrhage	1	1.7%
• DVT	4	6.8%
• Neurological (Convulsions)	1	1.7%
Mortality	0	0.0%
Total	8/58	13.7%

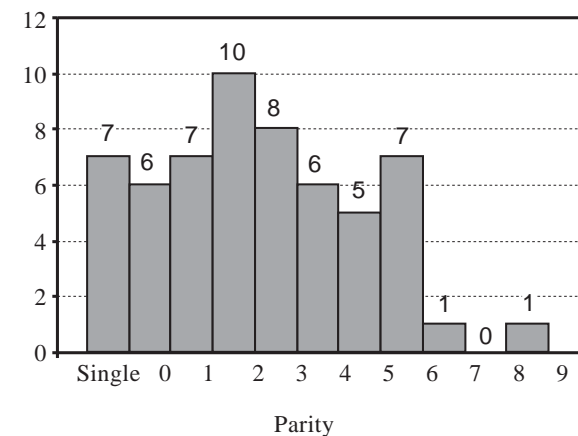


Fig. (2): Patients' marital status and parity.



Fig. (3): Panhystrectomy and omentectomy (R0).

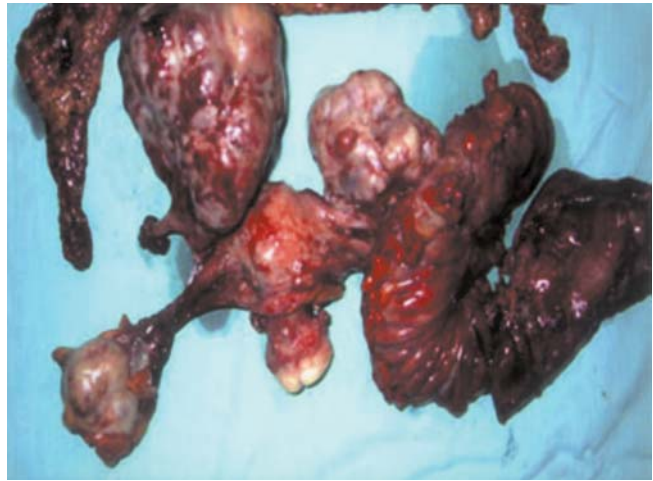


Fig. (4): Panhystrectomy with supracolic and infracolic omentectomy and sigmoid colectomy (R1).



Fig. (5): Panhystrectomy with supra and infracolic omentectomy for bilateral ovarian tumor (R1).



Fig. (6): Panhystrectomy with supra and infracolic omentectomy for bilateral ovarian tumors (R1).



Fig. (7): Huge ovarian mass after maximum cytoreduction (R2).

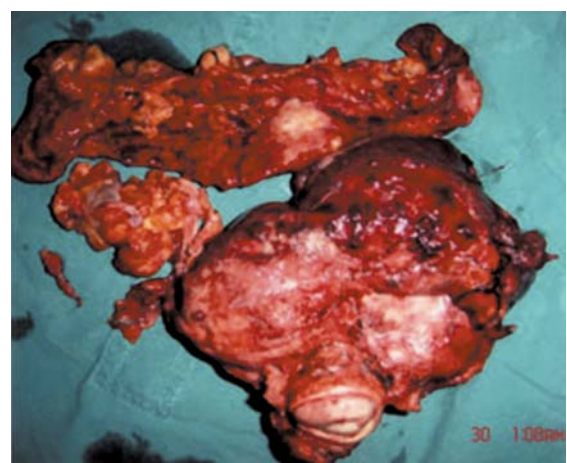


Fig. (8): Panhystrectomy, omentectomy and pelvic lymphadenectomy for large ovarian tumor (R2).

DISCUSSION

Diagnosis and management of ovarian cancer is one of the most important challenges in oncology as this disease is a common gynecological problem and it is the leading cause of death among all gynecological malignancies [2]. The main problem in the management of ovarian cancer is that there is no effective means to screen for ovarian cancer, thus most women are usually diagnosed with advanced disease with subsequent difficulty in treatment with high rate of recurrence and bad prognosis [1]. The effective ovarian cancer management is an integrated, multimodality approach involving different surgical procedures and different protocols of chemotherapy [8].

Tremendous advances have been made in chemotherapy for ovarian cancer over the past 20 years, but surgery remains the cornerstone of effective management of the disease [6].

Ovarian cancer is unusual among solid tumors in that surgical reduction of tumor volume is highly correlated with a prolongation of patient survival. Patients who are left with little or no visible residual cancer at the end of their initial surgery enjoy a dramatically improved survival time over women who have bulky residual tumor at the end of initial surgery or who are treated by chemotherapy alone. A review of published studies of surgical cytoreduction revealed that women with less than 2cm of residual tumor at the end of initial surgery had a median survival time of 37 months, whereas women with bulky residual tumor had a median survival of 17 months [10].

In our study, 58 patients presented to NCI, with stage III and VI epithelial tumors. Cytoreductive surgery was performed for 43 patients as we believe that proper cytoreduction and postoperative chemotherapy are the key for maximum disease control and improvement of survival in stage III and VI according to FIGO classification. In our patients, the plan of surgical management was to perform maximum cytoreduction which was achieved in 19 patients (R0) and less debulking (R1) in 17 patients and (R2) in 15 patients, where (R0) cytoreduction could not be achieved. A recent trend in treatment of advanced and recurrent cases is to do surgical cytoreduction and perioperative (intraoperative or early postoperative) intraperitoneal chemo-

therapy [6, 11]. This treatment modality is not yet tried in our patients and we hope to improve our results in the near future.

Interval surgical cytoreduction can be performed in patients who do not receive optimal cytoreduction. They can receive two to four cycles of chemotherapy to be followed by optimal cytoreduction [12]. We had 5 patients who had this kind of management. Chemotherapy as neoadjuvant can be given in advanced disease which is suspected radiologically or in patients who cannot tolerate extensive surgery [13].

There is general agreement according to most of the literatures that aggressive cytoreductive surgery conveys a significant benefit to patients who had successful surgeries with accepted complication rate and minimal mortality [14, 16]. We had no mortalities, while morbidities were 8.6% and 13.7% intraoperative and postoperative, respectively.

Cytoreductive surgery is now considered as a crucial component of the management of cancer of the ovary. Surgical cytoreduction of ovarian cancer has been associated with an increase in survival in all settings in which it has been studied, mainly in patients with chemosensitive disease, mainly in stages III and VI. These were defined as inoperable before, but nowadays there is marked improvement in survival after cytoreductive surgery [17, 18].

In our series patients were followed up during the period of study with a local recurrence rate of 22.41%. All recurrences occurred in patients left with residual tumor. We hope that introduction of intraperitoneal hyperthermic chemotherapy in advanced cases at NCI will achieve better results, although long term follow up is needed to confirm the combined effect of the cytoreductive surgery and systemic and hyperthermic intraperitoneal chemotherapy on local disease control and overall survival.

Conclusion:

Surgery remains a major line of therapy in ovarian cancer. Extensive procedures to maintain an R0 result are crucial to reach a satisfactory local disease control. The NCI, as well as all tertiary cancer centers, has an important role in providing this quality of surgery especially in advanced cases. Chemotherapy, in addition to surgery, dramatically improves survival espe-

cially in advanced cases. The close coordination between surgery and chemotherapy in the form of Intra-Peritoneal Hyperthermic Chemotherapy (IPHC) represents a hope for patients with advanced disease and should be introduced and established in all major cancer centers.

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