The Role of Completion Surgery in Ovarian Cancer

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Abstract

Introduction Patients referred with inadequately staged ovarian malignancies present a clinical dilemma. We report our experience with completion surgery in ovarian cancer. **Aims and Objectives** To determine the benefits and risks of completion surgery in women with ovarian cancer who presented after having had inadequate primary surgery. **Methods** A retrospective case series of 30 women with ovarian cancer and one with fallopian tube cancer who had inadequate primary surgery underwent completion surgery at gynaecologic oncology unit in a tertiary level hospital in Tamil Nadu, India. Electronic medical records of patients with ovarian cancer who underwent completion surgery between January 2011 and September 2014 for ovarian were reviewed. Forty-five patients with initial inadequate

surgery were identified of whom 31 underwent completion surgery; the remaining 14 did not return to our hospital.

Results Thirty-one women with a mean age of 37 years (17–53) and median parity of 2 (0–4) with inadequately staged ovarian malignancy underwent completion surgery. Complex ovarian mass was the most common indication for initial surgery (94 %). The tumours were epithelial in 27 (87 %), germ cell in 3 (10 %) and sex cord stromal in 1 (3 %). In view of extensive disease at presentation, 19 % (6/31) were referred for neoadjuvant chemotherapy and underwent interval debulking. With regard to surgical complexity, 52 % (16/31), 38 % (12/31) and 10 % (3/31) underwent simple, intermediate and complex surgeries, respectively. Optimal cytoreduction (R0 and R1) was performed in 25 patients (81 %). Twelve (39 %) had upstaging of disease. Six patients required no further adjuvant treatment following surgical restaging. Complications included bladder injury (1), iliac vessel injury (1) and surgical site infections (2). During the study period of 45 months, 7 patients (23 %) presented with disease recurrence. There were 2 recorded deaths.

Conclusions In inadequately staged ovarian malignancies, completion surgery should be considered based on the patients' performance status and disease assessment. Considering the low specificity of imaging and Ca 125, completion surgery provides information to plan adjuvant therapy, besides allowing optimal cytoreduction but delays initiation of adjuvant therapy.

Keywords Ovarian cancer · Primary inadequate surgery · Completion staging

Introduction

Ovarian cancer is a common malignancy affecting Indian women and is an important cause of morbidity and mortality especially in middle-aged women. The age-standardized rate in a survey conducted between 2001 and 2006 in India ranged from 0.9 to 8.4 per 100,000 women [1]. There seems to be increasing age-specific incidence rates in many age groups over the years [1].

The current standard of care for ovarian cancer is maximal debulking surgery and tailored platinum-based chemotherapy. There is now clear evidence that for residual disease, post-surgery is an important prognostic variable in overall survival [2], besides being the only modifiable prognostic factor. Besides debulking the disease, surgery allows accurate staging. Primary assessment and debulking by a gynaecologic oncologist improve survival in these women [3]. In the light of the above, patients operated for a complex ovarian mass, with a post-operative

diagnosis of ovarian cancer and an inadequate surgery, present a clinical dilemma: to reoperate followed by chemotherapy or to get on with chemotherapy followed by observation or completion surgery. The current NCCN guidelines recommends completion surgery in stages 2–4 and options of completion surgery or chemotherapy in stage 1 depending on the clinical situation and substaging. However, the decision to manage inadequately staged patients depends on the clinical situation, patients' performance status and the gynaec oncologist's expertise. There is limited literature with regard to completion surgery. We report our experience in managing inadequately staged ovarian cancer, in a tertiary care hospital, situated in South India.

Aims and Objectives

To determine the benefits and risks of completion surgery in women with ovarian cancer who present after having had inadequate surgery.

Methods

Design

A retrospective case series of 31 women with ovarian cancer who had inadequate primary surgery subsequently underwent completion surgery.

Setting

The study is carried out in a gynaecologic oncology unit in a tertiary level hospital in Tamil Nadu, India.

Patients

The ovarian cancer database of the gynaecologic oncology unit was used to identify patients who underwent initial surgical procedure and were diagnosed to have an ovarian malignancy subsequently. Between January 2011 and September 2014, 45 patients with initial incomplete surgery were identified of whom 31 consented to undergo completion surgery. Electronic medical records of these 31 patients were reviewed. Fourteen patients with inadequate primary surgery for ovarian malignancy refused completion surgery and did not follow up further with the hospital. During this time period of 45 months, 418 women with ovarian malignancies were seen during this period of whom 384 underwent surgery.

Results

Thirty-one women with a mean age of 37 years (17–53) and median parity of 2 (0–4) with inadequately staged ovarian malignancy consented for completion surgery. Majority of them (17/31, 55 %) hailed from East India (Table 1). Most of them had no associated risk factors. One had family history of gastrointestinal and gynaecological malignancy, and 2 were treated previously for secondary infertility. Eight-four per cent of the tumours were of epithelial origin (26/31), 10 % (3/31) were of germ cell origin, and 3 % (1/31) were of sex cord origin. One patient with inadequate surgery for fallopian tube cancer presented for completion surgery.

Complex ovarian mass was most common indication for initial surgery (29/31, 94 %), which was associated with distension in 6, ascites in 1, acute abdominal pain in 2 and pregnancy in 3. Other indications for surgery included hydrosalpinx and large uniloculated ovarian cyst (Table 2).

The previous surgeries performed included: laparoscopic cystectomy/oophorectomy (5), LAVH (1), open

Table 1 Demographic details

Demographic characteristics	Results (n = 31)
Mean age	37 (17–53)
Median parity	2 (0–4)
<i>Region of origin</i>	
North India	1 (3 %)
East India	17 (55 %)
Central India	1 (3 %)
South India	9 (29 %)
Bangladesh	3 (10 %)
<i>Associated risk factors</i>	
Diabetes	1 (3 %)
Hypertension	4 (13 %)
Diabetes and hypertension	1 (3 %)
Secondary infertility	2 (6 %)
Family history of GI/gynaecological/breast malignancies	1 (3 %)
<i>Histological type of tumours</i>	
Epithelial	26 (84 %)
Serous	14
Mucinous	7
Endometroid	2
Clear cell	1
Mixed	1
Borderline	1
Germ cell (mixed)	3 (10 %)
Sex cord (granulosa cell)	1 (3 %)
Fallopian tube (epithelial)	1 (3 %)

Table 2 Details of primary surgery

Details of primary surgery	Results (n = 31)
<i>Indication</i>	
Complex ovarian mass	29 (94 %)
Associated with distention	6
Associated with ascites	1
Associated with pregnancy	3
Associated with acute abdomen	2
Large uniloculated ovarian cyst	1 (3 %)
Hydrosalpinx	1 (3 %)
<i>Primary surgery done</i>	
Laparoscopic procedures	
Unilateral adnexectomy	4
Ovarian cystectomy	1
Laparoscopic assisted vaginal hysterectomy	1
Laparotomy	
Ovarian cystectomy	4
Unilateral adnexectomy	16
Hysterectomy with adnexectomy	5
<i>Operative findings</i>	
Operative findings unavailable	9 (29 %)
Operative findings available	22 (71 %)
Surgical/biopsy findings suggestive of metastatic disease	6 (20 %)
Mean duration from primary surgery to presentation	49 days (7–275)
<i>Presumed stage</i>	
Stage 1	16/21 (76 %)
Stage 2	1/21 (5 %)
Stage 3	4/21 (19 %)

cystectomy (4), unilateral adnexectomy (16) and hysterectomy with unilateral or bilateral salpingo-oophorectomy (5). The average duration from initial surgery to presentation to the outpatient department was 49 days (7–275). Four patients had the initial surgery in our hospital. The operative findings at initial surgery were available for 22 patients, of whom one did not have slides and blocks for pathology review. Only the pathological blocks, slides and accompanying biopsy report were available for 8 of the 9 patients for whom operative details were unavailable. Six (6/31, 20 %) patients had surgical/histological evidence of metastatic disease following initial surgery. Seven of 16 apparent stage 1 tumours had documented capsule rupture and spill during surgery. Besides the 16 with apparent stage 1 disease, there were 1 presumed stage 2 and stage 4 with stage 3 among the 21 who had operative findings and biopsy documentation of initial surgery available.

Following initial assessment, 6 (19 %) patients were referred for neoadjuvant chemotherapy in view of extensive

Table 3 Details of completion surgery

Details of completion surgery	Results (<i>n</i> = 31)
Mean duration from initial surgery to completion surgery	78 days (16–305)
Interval debulking	6 (19 %)
<i>Surgery complexity score</i>	
Low	16 (52 %)
Intermediate	12 (38 %)
Complex	3 (10 %)
<i>Residual disease</i>	
R0	21 (68 %)
R1	4 (13 %)
R2	6 (19 %)
Operative complications	3 (10 %)
Intraop bladder injury	1
Intraop iliac vein injury	1
Superficial surgical site infection	1
Upstaging of disease condition	12 (39 %)
<i>Final surgical stage</i>	
Stage 1	14 (45 %)
Stage 2	2 (7 %)
Stage 3	15 (48 %)
Requirement for post-operative chemotherapy	25 (81 %)

disease and underwent interval debulking (Table 3), 4 of whom had documented metastatic disease at initial surgery. The mean duration from initial surgery to completion surgery was 78 days (16–305) in the remaining 25.

With regard to surgical complexity, disregarding the initial surgery, 52 % (16/31), 38 % (12/31) and 10 % (3/31) underwent simple, intermediate and complex surgeries, respectively. Four patients had fertility preservation surgery. Optimal cytoreduction (R0 and R1) was performed in 25 patients (81 %). Ancillary procedures done to obtain optimal cytoreduction included diaphragm peritonectomy, rectosigmoid resection and stapled anastomosis, colostomy, small bowel resection and anastomosis. There was one intraoperative bladder injury and one iliac vein injury that were repaired during the operation. One patient had superficial surgical site infection, post-operatively. Twelve (39 %) had upstaging of disease, 7 following initial assessment (of whom 3 underwent interval debulking) and 5 following completion surgery. Five of 16 presumed stage I disease were upstaged (31 %). Following completion surgery, 14 (45 %) patients were assigned to FIGO stage I, 2 (7 %) to stage II and 15 (48 %) to stage III. Six patients with a final FIGO stage 1a did not require adjuvant therapy following completion surgery.

During the study period of 45 months, 7 patients (23 %) presented with disease recurrence, 5 of whom could not be

Table 4 Post-surgery follow-up

Follow-up details	Results (<i>n</i> = 31)
Median follow-up	6 months (0–36)
Number of patients who came for follow-up	23 (74 %)
Disease recurrence	7 (23 %)
Deaths	2 (6 %)

contacted, one was reported to have died of the disease, and one is on second-line chemotherapy. The median follow-up was 6 months (0–36 months). Twenty-three of the thirty-one patients (74 %) came for at least one follow-up (Table 4).

In summary, 25 (81 %) of the 31 with prior inadequate surgery underwent immediate completion surgery and 6 (19 %) underwent interval debulking. Optimal cytoreduction was performed in 81 % (25/31), and 12 had upstaging of disease (39 %). Six patients did not require adjuvant chemotherapy. During the study period, there were 7 patients with disease recurrence, of whom 2 died.

Discussion

Since 1975, many studies, though retrospective in nature, have consistently shown improved survival outcomes with optimal cytoreduction and the prognostic significance of residual disease in ovarian cancer [4]. Based on the above, the current standard of care for ovarian cancer is primary debulking surgery even in patients with advanced but operable disease. Primary debulking surgery, theoretically, besides allowing accurate staging of disease, permits cytoreduction, thereby relieving patient's discomfort due to bulky disease and improving response to chemotherapy, and decreasing the risk of developing drug resistance to chemotherapeutic agents. Though ovarian cancer is the most lethal of all gynaecological malignancies, there seems to be an improvement in 5-year survival rates over the past 3 decades with surgical advances in obtaining optimal cytoreduction and medical advances in chemotherapeutic schedules and drugs [5]. As per Chi et al. [6], incorporation of extensive upper abdominal procedures to obtain increased optimal cytoreduction rates significantly improved 5-year progression-free survival (from 14 to 31 %: hazard ratio, 0.757; 95 % CI 0.601–0.953; *P* = 0.01) and 5-year overall survival (from 35 to 47 %) in stage IIIc and stage IV cancers.

In apparent early-stage ovarian cancer with disease apparently confined to the ovaries, lymph node involvement is reported to be around 9–25 % depending on the technique used [7]. Isolated extra-ovarian microscopic involvement of omentum alone is found to be 2–7 %,

whereas in apparently early-stage epithelial ovarian cancer, microscopic disease in the omentum has been reported in 0–22 % of the cases [8]. Surgical staging upstages disease in apparent early stage in 30 % of the cases [9], and optimal cytoreduction reduces rates of recurrence and improves survival in these women.

Thirteen to twenty-one per cent of women undergoing surgery for a complex ovarian mass will have an underlying ovarian malignancy [10]. When the diagnosis of ovarian malignancy is revealed only post-operatively when the biopsy report is followed up, there are many issues to contend with. Intraoperative cyst wall rupture and fragmentation of large tumour during laparoscopic delivery increase the risks of intraperitoneal and port site metastasis which are not reduced with surgical restaging. The other problem faced is the time lapsed from initial surgery to presentation to the gynaecologic oncologist as seen in our study, which possibly permits spread of the disease. The waiting time for completion surgery from presentation can compound the patient's anxiety besides the financial implication of a second surgery in a country where most patients are uninsured. The technical difficulties faced during completion surgery due to initial surgery are another issue. Intraabdominal adhesions due to prior surgery can be anticipated. Two patients in this series had retroperitoneal fibrosis leading to iliac vein injury in one and inaccessibility into the retroperitoneum for lymphadenectomy in another patient. These technical difficulties can increase operative time, lead to intraoperative and postoperative morbidity and can compromise cytoreductive rates. In the young patient when fertility preservation is desired, chemotherapy could be avoided after completion surgery. But on the down side, the adhesions as a result of a second operative procedure can compromise fertility.

In contrast to the above, completion surgery can be justified from facts extrapolated from primary debulking surgery and completion surgery may have a diagnostic, prognostic and a therapeutic role in patients who have had prior inadequate surgery for ovarian malignancy. In its diagnostic role, completion surgery permits accurate staging. Imaging cannot be substituted for completion considering the low specificity of imaging in apparent early disease [11] and post-op artefacts which can pose as disease in these patients. Four patients in this study in whom preoperative CT scan showed residual disease had no residual disease following completion staging, whereas one patient had peritoneal metastasis when the CT scan reported "no residual disease". Tumour markers also have poor sensitivity and specificity in early disease. CA 125 can be elevated in post-operative patients. Five patients in this study had elevated CA 125 but had no disease during

completion surgery. The diagnostic role of completion surgery identifies patients in whom chemotherapy can be avoided and also prognosticates patients based on the stage and residual disease. Completion surgery allows optimal cytoreduction and hence its therapeutic role. In advanced disease, neoadjuvant chemotherapy followed by completion surgery may be an option.

However, the evidence on the survival benefit conferred by completion surgery is unclear as the data are mostly from retrospective small studies. In the study by Bacalbasa et al. [12], patients beyond stage IIIc who had inadequate surgery had reduced survival rates regardless of the subsequent approach and recommended interval debulking over upfront surgery. However, of the 99 patients recruited in the study, 62 patients had only a biopsy at the initial surgery. Stier et al. [9] recommended completion staging only in patients who would benefit from optimal cytoreduction. Though it provided important prognostic information, the authors concluded that it was of little benefit to patients who already required chemotherapy. Survival benefit was not looked at.

On the contrary, Grabowski et al. [13] reported a median survival time of 53 months in women with stage IIIb and beyond, who underwent upfront completion surgery after primary inadequate surgery, which was comparable to the median survival of those who underwent primary upfront surgery in the same centre. Higher complication rate was reported in women who underwent interval cytoreduction compared to upfront completion surgery (26.9 vs. 9.1 %), and the study recommended upfront resurgery over interval cytoreduction when feasible. Gultekin et al. reported significantly higher median survival in those patients who underwent upfront completion surgery over those who underwent primary debulking surgery for unexplained reasons (39 vs. 25 months, $P = 0.03$) [14]. Residual disease was the most important prognostic factor. Oksefjell et al. [15] similarly concluded that primary radical surgery was the most important prognostic factor who received complete tumour resection with no residual disease in both groups of patients who had undergone either upfront completion surgery or primary debulking.

Completion surgery therefore has a possible survival benefit as it allows optimal cytoreduction. Meta-analyses have shown that with each 10 % increase in maximal primary cytoreduction, a 5.5–6.0 % increase in median survival time was observed [4]. In our study, patients who refused completion surgery could not be followed up to assess survival benefit. In spite of completion surgery, 7 patients had recurrence of disease: 6 of them were of stage III c, one had stage I c disease and 3 had residual disease measuring more than 2 cm.

Laparoscopic restaging in apparent early-stage disease can be considered in referral centres but needs further evidence for substantiation [16].

Conclusion

Inadequately staged patients with ovarian cancer pose a clinical quandary to the gynaecologic oncologist. To avoid such situations, women with suspicion of ovarian cancer should be referred to specialized centres and preferably be operated by gynaecologic oncologists, to avoid patients undergoing a second operation and also increased risks of recurrence and death.

The benefits of completion surgery are as follows: it

- (1) allows accurate staging, thereby providing prognostic information,
- (2) permits selection of patients with apparent early disease for chemotherapy considering the low specificity of imaging and CA 125,
- (3) possibly has a theoretical survival benefit as it allows optimal cytoreduction.

On the downside, the disadvantages of completion surgery are as follows: it

- (1) delays initiation of chemotherapy in patients who require adjuvant treatment and also allows disease progression,
- (2) is associated with operative morbidity,
- (3) has no clear evidence of survival benefit,
- (4) is not always associated with optimal cytoreduction.

In conclusion, in a patient with inadequately staged ovarian cancer, considering the patients' performance status and disease assessment, after weighing the advantages and disadvantages, completion surgery should be considered. Upfront completion surgery can be considered if the patient is deemed fit and optimal cytoreduction can be performed. Completion surgery is recommended in all presumed early-stage disease as 30 % of them will be upstaged.

Compliance with Ethical Standards

Conflict of interest Vinotha Thomas, Anitha Thomas, Ajit Sebastian, Rachel Chandy and Abraham Peedicayil declare that they have no conflict of interest.

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