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Original Research Article

An intensive audit on 250 patients of advanced ovarian cancer to improve quality of care in a tertiary referral oncology centre in India

M. D. Ray*, S. V. S. Deo, Raja Pramanik, Premanand N.

Department of Surgical Oncology, IRCH, AIIMS, New Delhi, India

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***Correspondence:**
Dr. M. D. Ray,
E-mail: drmajormdrayaiimsdelhi@aiims.edu

ABSTRACT

Background: A clinical audit provides the framework to improve the quality of patient care in a systematic way. In this study, we intensively audited our 250 advanced epithelial ovarian cancer (EOC) patients aiming to improve our patient care.
Methods: Ambispective study of 250 patients of advanced EOC was done from our prospectively maintained computerized database in the department of surgical oncology, AIIMS, New Delhi from 2013 to 2020.We audited the demographic profile, treatment patterns, perioperative and survival outcomes in different subgroups.
Results: In this study, 83.6% stage III and 16.4% stage IV A. There was 62 (24.8%) upfront, 112 (44.8%) interval and 76 (30.4%) secondary group. 126 underwent cytoreductive surgery (CRS) and 124 CRS and hyperthermic intraperitoneal chemotherapy (HIPEC). There was 24.8% early and 8.4% late postop complications. Median follow up 50 months. Overall, the median disease-free survival (DFS) 39 months. PFS was 12 months among 68 patients with recurrence. Attrition rate 4%. In the upfront setting, the median DFS 44 months in CRS only group and DFS not reached (p=0.032) in CRS and HIPEC group still. In the interval setting, the median DFS 39 months in CRS only group and 44 months in CRS and HIPEC group (p=0.06). In recurrent setting, the median DFS 14 months in CRS group and 23 months in CRS and HIPEC group (p=0.02)
Conclusions: Audit is an integral part of any clinical practice. It teaches us to improve the quality of care and thereby better outcomes. We recommend 6 monthly clinical audits in any cancer treatment for better outcomes in future.

Keywords: Ovarian cancer, CRS, HIPEC, DFS, Clinical audit

INTRODUCTION

The incidence of EOC is increasing day by day. As per Globocan data, the worldwide incidence of ovarian cancer is 2,95,414 patients with a mortality of 62.55%.[1] In India, it is almost touching the incidence of carcinoma cervix. The prevalence may be much higher as most patients in rural India die without ante mortem diagnosis. Mostly because of the vague symptomatology and fairly advanced stage at presentation.

The current standard treatment consists of complete CRS followed by platinum-based chemotherapy. HIPEC into the peritoneal cavity at 41^0-43^0C for 60-90 minutes after complete cytoreduction, has become the advanced treatment modality with a five survival up to 50% but remarkable morbidity, mortality and cost is an issue.[2]

In this tertiary care center, most of patients are referred after receiving some form of treatment outside or in a complicated state. Thereby selection option is very limited to us. A clinical audit provides the framework to improve the quality of patient care in a systematic way. This study is unique and aims to provide the insight into the demographic profile, treatment patterns, perioperative and surgical outcomes in ovarian cancer patients in government setup.

METHODS

Ambispective study of 250 patients of advanced EOC was done from our prospectively maintained computerized database in the Department of surgical oncology, AIIMS, New Delhi from 2013 to 2020.We have selected operable stage III-IV A patients in three settings-upfront, interval and recurrent. We audited the perioperative outcomes in terms of perioperative morbidity, mortality and survival outcomes in terms of DFS of 250 patients We audited the demographic profile, treatment patterns, perioperative and survival outcomes in different subgroups. There attrition rate of 4%. Patients who lost to follow up were called telephonically and present status and survival updated. Institutional ethical committee clearance and informed written consent taken as per our institutional policy for this study. Data was analyzed using SPSS 2.0 software.

RESULTS

Demographics with modes of presentation

A total of 250 EOC patients were included in the study. The mean age at presentation was 48.28 years (19 to 80 years). There were 32 patients below 35 years. About 83.6% were stage III and 16.4% in stage IVA. There were 62 patients (24.8%) in upfront, 112 (44.8%) in interval and 76 (30.4%) in the secondary groups respectively. We had patients from all over India but predominantly from Delhi 106 (42.4%) and Uttar Pradesh 51 (20.4%).

About 84.8% (n=212) were referred and were symptomatic at presentation. In asymptomatic patients the malignancy was diagnosed on incidental imaging studies. Vague abdominal pain 47.6% (n=119) and abdominal distension 36.8% (n=92) were commonest presentation. Symptoms were present in 88% in primary, 45% in interval and 17% in recurrent setting. In recurrent settings symptoms are less and as diagnosed mainly on imaging or due to increased CA 125 levels on follow-up.

About the 17.6% patients had family history of malignancy (breast/ovarian 11.6% and endometrial cancer 0.02%). 68% patients had ECOG-1 and 32% had optimized ECOG-2 performance status. 27.2% patients had significant ascites (17.6% grade 2 and 9.6% grade 3). Only three patients needed therapeutic tapping to relieve dyspnea at presentation.

About 38.7% had hemoglobin between 6.1 to 8 gm/dl. In patients who underwent complete cytoreduction (CC-0 and CC-1) the mean CA125 value are 467 and 1267 U/ml in upfront group, 78 and 322 U/ml in interval group,175 and 204 in secondary group respectively.

We routinely do retroperitoneal lymph node dissection in all cases as nodes act as sanctum site and harbor microscopic disease which may give rise to late recurrences after HIPEC. There was substantial stage migration noted in stage IIIA (from 35 patients detected to retroperitoneal nodes by CT down staged to stage IIB/ less in 12 patients). This suggests need for routine retroperitoneal lymph node dissection in this subset as it would help in accurate pathological staging and prognostication.

Our post-operative mortality was 10 patients (4%). In primary group 3, interval group 3 and recurrent group 4.

Treatment patterns and outcomes

On the basis of the disease burden, we stratified the patients either for primary CRS or for Neoadjuvant chemo therapy. Even in IIIC patient we like to perform upfront if it fits our operability criteria. Usually, we take <20 PCI for primary surgery. In recurrent setting we look for biology of the disease. If PCI is <10 we perform secondary CRS or CRS and HIPEC. Absolute contraindications are performance status >2, acute or chronic DVT, stage IVB with parenchymal involvement of liver or spleen and transmural small bowel involvement, extensive involvement of root of mesentery where ≥2 bowel segmental resections are needed, small bowel resection requiring >2 meters and ≥2 cm nodes at superior mesenteric artery, behind the porta hepatis or renal hilum. Relative contraindications are age >70 years, serum albumin ≤2 gm/dl, CA-125 >2000 U/mL, extensive upper abdominal disease, involvement of the diaphragm or lesser omentum, massive malignant pleural effusion, chemo-resistant tumor biology: clear cell, mucinous histology, CT PCI >20, young patient where biology seems aggressive and expected blood loss >1.5 L.

126 (50.4%) underwent CRS only and 124 (49.6%) patients underwent CRS and HIPEC. CC-0 was achieved in 84.4% and CC-1 in 15.5% patients. Number of primary CRS was 42.6% (n=29), CRS and HIPEC was 53.5% (n=33). Number of interval CRS was 58.92 % (n=66), CRS and HIPEC was 41.08% (n=46). Secondary CRS was 40.7% (n=31) and CRS and HIPEC was 59.3% (n=45).

Logistic issue is the main determining factor for non-offering of HIPEC even after optimal CRS. Alternately we started early post-operative intraperitoneal chemotherapy (EPIC) which has not been included in this audit.

We have included only Clavien-Dindo grade III, IV complications. The complications were classified as early within 30 days and late from 31 to 90 days. There was 24.8% early and 8.4% late postoperative complications as listed in Table 1-3.

Survival outcomes in advanced ovarian tumors

The median follow up time was 50 months. Overall, the median DFS of 250 patients was 39 months (Figure 1A) 27.2% (68 patients) had a disease recurrence on follow-up. In primary group 14 patients, Interval group 20 patients and in secondary group 34 patients had disease recurrence for those with recurrence, the median PFS was 12 months

only (Figure 1B). Overall, the median DFS was higher in primary (44 months) followed by interval (38 months) and secondary group (23 months) (Figure 1D).

Table 1: Frequency of early and late complications in different settings.

Variables	Primary (%)	Interval (%)	Recurrent (%)
Early complications	19 (23.17)	10 (19.39)	6 (15.38)
Late complications	3 (5)	5 (6.41)	Negligible

Table 2: Early postoperative complications, (n=24.8%).

Early complication	N	Percentage (%)
Deep SSI	8	3.2
Ureteric reconstruction	8	3.2
SAIO/paralytic ileus	7	2.8
Enterocutaneous fistula	5	2
Intraabdominal collection	4	1.6
Burst abdomen	4	1.6
Chyle leak	2	0.8
Lymphocele	2	0.8
Subclavian v thrombosis	1	0.4
Bedsore	1	0.4
Bladder repair	5	2
Acute kidney injury/ derangement of function	7	2.8
Post-op bile leak	1	0.4
Re exploration (any cause)	7	2.8

Table 3: Late postoperative complications, (n=8.4%).

Late complications	N	Percentage (%)
Incisional hernia	3	1.2
Ureteric stricture	2	0.8
Lymphocele	5	2
SAIO	4	1.6
Ascites (nonmalignant)	2	0.8
DVT	3	1.2
Entero cutaneous fistula	2	0.8

Then we did subgroup analysis to see the outcomes of CRS and HIPEC when compared to CRS only in different settings viz., upfront, interval and secondary. In the upfront group, 42.6% (n=29) underwent CRS only and 53.5% (n=33) underwent CRS and HIPEC. The median DFS was 44 months (CRS only) and not reached in CRS and HIPEC group. The difference was statistically significant with p=0.032.

In the interval group 58.92% (n=66) underwent CRS only and 41.08% (n=46) underwent CRS and HIPEC. The median DFS was 39 months (CRS only) and 44 months in CRS and HIPEC. The difference was not statistically significant with p=0.06.

In the secondary group, 40.7% (n=31) underwent CRS only and 59.3% (n=45) underwent CRS and HIPEC. The median DFS was 14 months (CRS only) and 23 months in CRS and HIPEC. The difference was statistically significant with p=0.02.

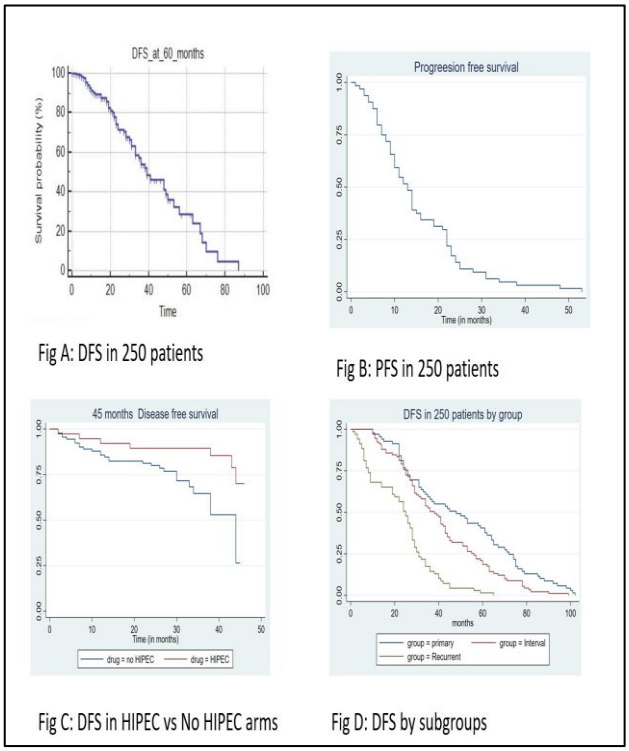

Figure 1: (A) Disease free survival in 250 patients, median DFS was 39 months, (B) median progression free survival of 12 months among those who had a recurrence on follow up (68 patients), (C) median DFS in CRS only arm was 38 months and in HIPEC arm median DFS not reached (at 50 month follow up) and (D) DFS by subgroups (44 months in primary, 38 months in interval and 23 months in secondary group).

DISCUSSION

Ovarian cancer is the most lethal cancer of the female genital tract. In the United States, it is responsible for more cancer deaths than all other gynecologic tumors.[1] Malignant epithelial tumors are the most common type of ovarian cancer and comprise almost 90% of cases.[3]

Various risk factors described in developments of carcinoma ovary including family history of the disease, infertility and environmental factors. Endometriosis is the prominent risk factor for developing endometrioid and clear cell variety. But most of our patients had sporadic cancer. About 17.6% patients had a family history of malignancy. The treatment of ovarian cancer has been based mainly on tumor grade and stage, but it is now

apparent that the histologic subtype is just as important as in patient management. The various histologic subtypes are different in terms of risk factors, precursor lesions, clinical course, patterns of spread, molecular genetics, response to conventional chemotherapy, and prognosis.[3-5]

If we see the natural history of ovarian cancer, the disease is confined to the peritoneal cavity for a long time. Distant metastasis beyond the abdomen is only 2 to 5%. As there is a plasma peritoneal barrier, systemic chemotherapy is not as effective as expected. The goal of CRS is to removal all tumor deposits (CC-0) or residual tumor deposit less than 2.5 mm (CC-1). The ability to achieve complete cytoreductive depends on the Peritoneal carcinomatosis index and the clinical setting viz., upfront, interval and secondary settings. HIPEC is the most advanced form of intraperitoneal treatment in selected EOC patients.

HIPEC (Hyperthermic intraperitoneal chemotherapy) delivers heated chemotherapy into the peritoneal cavity at 41-43^{0}C for 60-90 minutes after complete cytoreduction. Hyperthermia exhibits a selective cell-killing effect in malignant cells by itself, potentiates the cytotoxic effect of certain chemotherapy agents, and enhances the tissue penetration of the administered drug (5-7 mm).[6] The nomenclature of HIPEC depends on the timing of the intervention in relation to systemic chemotherapy It is called as Upfront/ primary CRS and HIPEC -when performed primarily, Interval CRS and HIPEC- when performed after 3 to 6 six cycles of NACT and secondary CRS and HIPEC-when performed for patients who have recurrence after CRS or CRS and HIPEC. It is now imperative to identify the most optimum use of HIPEC in conjunction with targeted biological therapy amidst the background of differential genetics and epigenetics and multi-omics of ovarian cancer which has to be explored on urgent basis.

Among the larger series, the reported grade III/IV GI complication rate ranges between 4.5 to 19%.[7-11] Small bowel perforations and anastomotic leaks are the most common and clinically significant. A possible explanation for digestive non-anastomotic perforation could be partial-thickness mechanical damage to intestinal surfaces, focal heat injury at the tip of the inflow catheters, suctioning effect of the outflow catheter, or postoperative shrinking of infiltrating metastatic nodules on the intestinal wall because of the antiblastic effect of HIPEC.

From the audit we could find that the risk for such complications could be minimized by careful lyses of adhesions and dissection, with judicious use of the ball-tip electro-cautery when used for dissection of superficial peritoneal lesions. In our study, GI complications occurred in 5.2% in the early postoperative period and 2.5% in the late post-op period. Several studies have reported the incidence of grade 3/4 pulmonary complications to be in the range of 10-16%.[12-14]As expected, peritonectomy of abdominal diaphragmatic surfaces significantly increases post-operative pleural effusions, particularly in absence of systematic thoracic drainage.[15,16] However, this strategy can reduce but not abolish the intrinsic risk of pleural effusion, which remains the second most common pulmonary complication.[12] Patients undergoing peritonectomy procedures have a significant risk of postoperative infectious complications and pneumonia is approximately reported in 3.2-10 % of patients .[15-16] In our study, we did not have any grade3/4 pulmonary complications. Several studies showed that pulmonary complications can be reduced by local experience, better peri-operative fluid and glycemic control, and multi-disciplinary management of patients undergoing CRS and HIPEC.[17-20]

Other less frequent grades 3/4 complications can occur after CRS and HIPEC such as renal insufficiency (2-4%), venous thromboembolism (4-4.4%), urinary tract infections, vascular access infections.[22-25] About the 2% of our patients had grade II, grade III neutropenia and managed successfully. In our study, derangement in renal function was noted in 8 patients (3.2%). ureteric stricture occurred in two patients (0.8%). Subclavian vein thrombosis was noted in one patient in the early postoperative period and lower limb DVT was noted in 3 patients as late complications. In our institute, we follow ERAS protocol in addition to Injection Dalteparin starting 12 hours before surgery, mechanical DVT pump intra-op and postoperatively along with early mobilisation. DVT was found to be associated with obesity, higher intra-op PCI. Re-exploration from any cause was warranted in 7 patients.

The Chicago consensus working group guidelines recognize and address the emerging need for increased awareness of the appropriate management of peritoneal surface disease and define the process standards for tertiary care Institute dealing with the management of peritoneal surface malignancies. Our institute is a high-volume centre performing more than 12 CRS and HIPEC per surgeon per year. Our 30-day mortality rate is 1.64%. The mean ICU stay is 1.62 days and mean hospital stay is 8.54 days. Our ostomy rate is 6.4%, transfusion rate is 20% and re-admission rate is 8.9%. The targets are within the limits prescribed by the consensus working group.[26]

We recognize the retrospective nature of our study. Our patient selection criteria for upfront/interval settings were PCI ≤15 and in secondary settings PCI <8. Most of our patients were referred to us after surgery/ chemotherapy from private centres. We encourage pre-habilitation of patients at first point of contact in outpatient clinics. Treatment strategy depends on our NACT policy, performance patients status and tumor board opinion. The DFS in our study was defined as the time interval between the date of surgery and the date of recurrence.

In Van Driel study on 245 patients, RCT on stage III c EOC, the RFS was 14.2 months in CRS and HIPEC arm versus 10.7 months in CRS arm. There was 27% morbidity in HIPEC arm. They used 100 mg/m^2 of cisplatin.[27] In

another RCT including 120 patients of recurrent stage IIIc/IV EOC by Spiliotis et al, The OS was 26.7 months in HIPEC arm compared to 13.4 months in CRS arm. Also, with the addition of HIPEC the 3- year OS increased to 75% from 18%.[28] In previous studies on recurrent OC, 5-yr survival increased from 17 to 58% with addition of HIPEC and also CRS+ HIPEC increases Recurrence-free interval from 24 upto 48 months.

In a systematic review and meta-analysis on survival benefit of HIPEC by Kim et al, HIPEC improved the DFS and OS in primary disease. However, subgroup analysis revealed that HIPEC did not improve OS but improved DFS in patients with residual tumors < 1 cm and no visible tumor. In recurrent disease, HIPEC was associated with better OS but not DFS.[29]

Similarly, in our study the addition of HIPEC improved the DFS in upfront and secondary groups. All of our patients underwent complete cytoreduction CC-0/CC-1 before HIPEC. Among those with recurrence after HIPEC, Peritoneal cancer index, achieving complete cytoreduction and upper abdomen disease burden are important prognostic factors.

In our audit, we learnt that most of the postoperative mortality can be prevented by proper pre-operative patient selection with emphasis on performance status, PCI and response to chemotherapy. Intraoperative meticulous dissection, decision whether to proceed further when are there are surprising intraoperative findings and taking into consideration the hemodynamic stability and need for vasopressor support before proceeding with HIPEC could help reducing morbidity and mortality. From this audit, we can see that biology is the king, selection is the queen which is very limited option in our premier Institute and our skill and experience and technique are the prince and princess. Major morbidity and mortality are to be audited between concerned surgeon and anesthetist team immediately, latest by within the week and inter departmental audit every 6 monthly to avoid preventable mortality and morbidity.

Strengths and limitations

The major strength is the real-world data in Government run tertiary care centre where proper case selection remains the key to survival outcomes. The major limitation is the retrospective nature of study and the attrition to follow up.

CONCLUSIONS

Despite of multimodality treatment, the 5-years survival of advanced ovarian cancer is dismal (only 15-30%). With the advent of HIPEC in different settings, primary, interval and recurrent settings, 5-years survival improved significantly (Up to 50 %). In this study, the DFS was shorter in interval setting when compared with upfront setting. The addition of HIPEC improved the DFS in the upfront and recurrent setting.

Audit is an integral part of any clinical practice. It teaches to improve the quality of care and thereby better outcomes. From our audit, we learnt our avoidable mistakes and started avoiding preventable factors from the very next treatment policy. Major morbidity and mortality are to be audited between concern surgeon and anesthetist team immediately, latest by within the week and inter departmental audit every 6 monthly to avoid preventable mortality and morbidity thereby better survival outcomes.

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