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RESEARCH ARTICLE

Evaluation of inadequately staged ovarian cancer patients referred to gynaecologic oncology center

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ABSTRACT

Objectives: To analyse the factors associated with lack of comprehensive surgical staging (CSS) for early stage ovarian cancers performed at non-oncological centers. **Materials and methods**: A total of 50 patients with histologically proven ovarian cancer, operated elsewhere and underwent completion surgery (CS) or interval debulking surgery (IDS) at our institute were included. Demographic characteristics, preoperative evaluation, operative notes and histopathology reports of other centers were collected. Investigations and management done at our institute were analysed. **Results:** Out of the 50 patients included in our study, 38 (76%) patients were operated by gynaecologist and 7 (14%) by general surgeons. Preoperatively, ultrasonography was done in 35 (70%), CT scan in 19 (38%) and tumor markers in 19 (38%) patients. Thirty five (70%) patients had complex and solid lesions. 31 (62%) patients were histologically proven epithelial ovarian cancers. None of the patients had undergone CSS and operative notes of 37 (74%) patients could not be retrieved. Only 12 (24%) patients presented to our institute within 2 weeks of primary surgery. At our institute, 26 (52%) patients underwent completion surgery and 23 (46%) underwent NACT followed by IDS. Out of 26 CS patients, there was upstaging of disease in 6 (23%) patients and 15 (57%) required adjuvant chemotherapy. **Conclusion:** Our study confirms the adverse impact of inadequate staging and management of oncological patients operated in a non-oncological center by general gynaecologists and surgeons. There is need of awareness among general gynaecologists and surgeons regarding importance of CSS and timely referral to oncological center.

Keywords: Ovarian neoplasm, referral and consultation, chemotherapy adjuvant.

Ovarian cancer is the most aggressive gynaecological cancer with a 5 year overall survival of 40% [1]. Disease free survival, progression free survival and quality of life depends on the initial surgery i.e. CSS. CSS is one of the important prognostic factors for patient's outcome [2-8].

Malignant ovarian lesions are often misdiagnosed as haemorrhagic cysts, endometriosis, tuboovarian abscess, fibroids, abdominal TB, etc. Majority cases of early stage ovarian cancers are mismanaged as benign ovarian lesion by gynaecologists and general surgeons due to lack of suspicion regarding cancer. Thus, the preoperative evaluation is not targeted to rule out malignancy. Gynaecologic oncologist consultation is rarely sought for. Most of these cases are operated as benign ovarian lesion and subsequent histopathology examination reveals carcinoma. Patients are then referred to gynaecologic oncology center (GOC) where they undergo further management in form of completion surgery (CS) or neoadjuvant chemotherapy (NACT) followed by debulking surgery. CS results in proper staging of ovarian cancer which further helps in deciding need for adjuvant therapy. It not only adds to morbidity and financial burden but also leads to emotional turmoil and is associated with poor prognosis. Many patients are referred late and those who are referred timely often approach the oncology center late, due to financial and logistical hurdles. Most of these patients

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present with advanced disease.

We conducted this study to evaluate the inadequately staged ovarian cancer patients referred to GOC.

Methods

This was a cross-sectional study in which we analyzed retrospective data from January 2016 to December 2020. 1831 patients of ovarian cancer were operated at our GOC out of which 50 were included in the study. These patients were primarily operated elsewhere and had histologically proven ovarian cancer. They further underwent completion surgery (CS) or interval debulking surgery (IDS) at our institute. Data was collected from patient records. We reviewed patients' demographic characteristics, preoperative workup, operative notes and histopathology reports of surgery which were done elsewhere. RMI (Risk of Malignancy Index) was calculated using preoperative reports of ultrasonography and CA125. All those histology slides and blocks were reviewed by onco-pathologist at our institute. Detailed history, clinical examination, tumor markers and imaging done at our institute were documented. Following tumor board discussion involving multi-disciplinary departments, patients who presented late after initial surgery or with advanced disease underwent NACT followed by IDS. Patients with presumed early stage were planned for completion surgery. Surgical plan was individualized based on age, fertility status, histopathology, etc. All resected specimens were evaluated by onco-pathologists. All surgeries were performed by trained gynaec-oncologist. Intraoperative findings were compared with the previous operative notes, if available & were restaged or upstaged. Study had been reviewed by the appropriate ethics committee and had been performed in accordance with the ethical standards described in an appropriate version of the 1975 declaration of Helsinki, as revised in 2000. Data analysis was done in SPSS version 25 and Microsoft Excel 2013.

Results

The average age of patients in our study was 41.1 years. Thirty six (72%) patients were younger than 50 years of age and 14 (28%) patients were above 50years of age. Thirty seven (74%) patients consulted gynaecologist and 7 (14%) consulted general surgeon. The most common presentation was pain in abdomen (28 patients, 56%) followed by AUB (10 patients, 20%). Table 1 describes the preoperative workup done by the consulting doctor. Out of 50 patients, RMI could be calculated in 19 patients. In 8 patients RMI was greater than 200. Majority of the patients (38 patients, 76%) were operated by gynaecologists and 7 (14%) patients were operated by general surgeons. None of the patients were operated by gynaecologic oncologist. Details of the surgery done elsewhere are tabulated in table 2. Out of 14 patients with age more than equal to 50 years, 4 (28%) patients underwent unilateral oophorectomy.

Table1: Preoperative workup done at other institutes

Categories	No. (%)
Tumor makers done	19 (38)
• Normal	7 (36)
• Raised	12 (64)
Biopsy (preoperative)	1 (2)
USG	35 (70)
CT scan	19 (38)
Imaging findings of the ovarian lesion	
Simple cyst	4 (8)
Complex cyst	10 (20)
Solid cystic lesion	11 (22)
Solid lesion	14 (28)
Unilateral	30 (60)
Bilateral	9 (18)
Imaging findings suggesting advanced disease	
Ascites	2 (4)
Distant metastasis	5 (10)
RMI-1 (Risk of Malignancy Index-1)	
>200	8 (16)

Thirty nine (78%) patients were referred by primary operating surgeon for further management in view of histological diagnosis of malignancy. Eight (16%) patients were referred by other doctor and 2 (4 %) were self-referrals. Most (36 patients, 72%) of the patients were not counseled regarding the need for repeat surgery or chemotherapy; they were referred to higher center only for consultation. Detailed operative notes were available in only

Table 2: Surgery done outside	No. (%)
Laparoscopy	11 (22)
Laparotomy	39 (78)
Vertical incision	15 (38)
Transverse incision	24 (62)
U/L Cystectomy only*	15 (30)
U/L Salpingoopherectomy (SO) only	6 (12)
TAH with U/L cystectomy *	1 (2)
TAH with U/L SO *	2 (4)
B/L cystectomy *	1 (2)
BSO only *	4 (8)
TAH B/L salpingectomy (hydrosalpinx) *	1 (2)
TAH BSO *	12 (24)
TAH BSO omentectomy with peritoneal biopsy or ascitic fluid cytology *	2 (4)
Inoperable	6 (12)
Additional procedures	
Peritoneal wash cytology	2 (4)
Ascitic fluid cytology	2 (4)
Omentectomy	2 (4)
Omental biopsy	4 (8)
Appendicectomy	1 (2)

*U/L - Unilateral, B/L - Bilateral, TAH - Total abdominal hysterectomy, BSO- Bilateral salpingoophrectomy

13 (26%) patients. Twelve (24%) patients presented to our institute within 2 weeks of referral, 16 (32%) patients between 2 weeks to 1 month and 22 (44%) patients presented after 1 month of referral.

Table 3: Details of upstaged patient after CS

Histology	Presumed stage post primary surgery done outside	Final stage after CS
NET *	1C	3C
Carcinosarcoma	1C	3C
Carcinosarcoma	1A	3B
Granulosa cell tumor	1C	3C

*NET- Neuroectodermal tumor

Twenty six (52%) patients underwent CS and 23 (46%) patients underwent IDS. Optimal debulking was possible in 38 (76%) patients of both CS and IDS. Average time duration between the surgeries performed elsewhere to CS at our center ranged from 20 – 210 days (median 70 days).

Out of 26 patients who underwent CS, 4 (15.3%) patients were upstaged, 17 (65%) required adjuvant treatment (chemotherapy) and 9 (35%) patients did not require any further treatment. Table 3 presents detailed analysis of upstaged patients.

Table 4: Management done at our institute

Histology	CS [n, (%)]	IDS [n, (%)]
Serous papillary (n=20)	6 (30)	14 (70)
Mucinous cancer (n=4)	3 (75)	1 (25)
Endometroid cancer (n=3)	2 (66)	1 (33)
Adeno cancer (n=4)	1 (25)	3 (75)
Granulosa cell tumor (n=8)	7 (87.5)	1 (12.5)
Borderline ovarian tumor (n=4)	4 (100)	0
Germ cell tumors (n=3)	0	3 (100)
MMMT * (n=3)	3 (100)	0
NET * (n=1)	1 (100)	0

* MMMT- Malignant mixed mullerain tumor, NET- Neuroectodermal tumor

Table 5: Relationship between time since primary surgery and recurrences or residual

Time since primary surgery	Number of patients presented with suspected residual or recurrences
≤ 1month (n=30)	6 (20%)
>1 month to ≥ 6 months (n=16)	5 (33%)
>6 months (n=4)	2 (50%)

Histological distribution of slides and blocks reviewed at our institute: Epithelial cancers (62%), granulosa cell tumors (16%), borderline tumors (8%), germ cell tumors (6%), carcinosarcoma (6%) and neuroectodermal tumor (2%).

The three patients with germ cell tumor presented late with recurrence and required chemotherapy followed by IDS. Table 5 describes relationship between residual or recurrence disease and time duration from primary surgery to presentation at our center.

Discussion

Comprehensive surgical staging for presumed early stage ovarian cancer has been described as an important prognostic factor in patients' outcome [9-15]. CSS involves midline incision, peritoneal washings, inspection and palpation of the abdominal cavity, peritoneal biopsies, bilateral salpingoophrectomy, total abdominal hysterectomy, at least infracolic omentectomy, appendectomy in case of mucinous carcinoma, and lymphadenectomy. It fulfills two pre-requisites for adequate therapy, namely complete removal of tumor tissue and identification of patients who need further adjuvant systemic therapy. The latter helps to avoid unnecessary treatment in those who do not need it and to provide adequate treatment to those who would probably benefit.

In our study 25 (50%) patients had solid cystic or solid lesions, 2 (4%) had ascites and 5 (10%) had advanced disease on imaging. None of the patients were operated by gynaecologic oncologist. Preoperative CT scan and tumor markers were done in only 19 (38%) patients. Triaging tools such as RMI, ROMA (Risk of Ovarian Malignancy Algorithm) score, IOTA (International Ovarian Tumour Analysis) and ADNEX (Assessment of Different NEoplasias in the adneXa) models were not assessed in any patients. Inadequate preoperative workup led to lack of suspicion resulting in lack of referral to gynaecologic oncologist before surgery.

RMI is an effective discriminating tool to diagnose the benign or malignant nature of pelvic mass before surgery. With a cutoff point of 200, the sensitivity, specificity, PPV, and NPV are 81%, 85%, 48%, and 96%, respectively [16]. When RMI is greater than 200, there in more than 75% risk of malignancy. Out of 50 patients, RMI could be calculated in 19 patients. In 8 patients RMI was greater than 200. These patients should have been referred to gynaecologic oncologist in the initial setting.

Laparoscopy surgery for ovarian cancer still remains controversial considering the unexpected tumor rupture or spillage, difficulty in tumor extraction and port-site metastasis etc [17]. In our study 11 (22%) patients underwent laparoscopy and among them, tumor rupture was noted in 7 (64%) patients which led to upstaging. Type of incision has very important role in comprehensive surgery for ovarian cancer. Vertical incision allows exploration of entire upper abdomen and pelvis. In our study only 19 (38%) patients had vertical incision.

Only 2 patients, operated elsewhere, underwent near complete CSS (i.e. TAH BSO omentectomy with peritoneal biopsy or ascitic fluid cytology). One patient had involvement of pelvic and para aortic lymph nodes and other patient had CA125 7200 U/L. In none of the patients frozen section or lymphadenectomy was performed. The reason behind it could be the lack of oncological surgical skill, lack of suspicion of malignancy & non-availability of frozen section facilities. Six (12%) patients operated outside were declared inoperable. In 2 patients, imaging had shown advanced disease i.e. omental infiltration and 4 patients had elevated CA 125 levels (514, 634, 273 and 555 U/L). Such patients would benefit from evaluation & surgery by expert surgeon trained in gynaecological oncology & surgeons' expertise plays a significant role in patient outcomes. Tracing the reasons behind lack of CSS was not the purview of our study but the contributing factors could be: 1. Lack of clinical suspicion regarding cancer among gyanecologist and surgeons, 2. Inadequate preoperative evaluation, 3. General gynaecologist are not trained for CSS.

We have observed that no standard referral protocols were practised. Majority of the patients were not counseled by the referring doctor regarding reason of referral and possible course of action therefore, patients had immense fear and anxiety while visiting the higher center. Even if patients were properly explained and counseled by referring doctor many turned up late. The reasons for patients' delay in seeking further treatment could be: 1. Most of the patients belonged to low socioeconomic strata, 2. Financial, logistic & linguistic barriers, partly due to illiteracy played an important role in such delays, 3. There were also social issues preventing the patient from seeking care at higher centers in cities. Proper operative notes of primary surgery were available in only 26% of patients in our study.

Thus, counseling, education and financial and logistic help can avoid delayed reporting of referred patients. Detailed operative notes are integral part of any surgery and they reveal a lot about the probable stage of disease, reason for inoperability, anticipation of difficulties in the completion surgery and help in deciding further course of treatment.

Twenty three (46%) patients underwent IDS at our institute because of following reasons: delay between primary surgery and reporting to higher center, recurrence or advanced nature of disease.

Out of 26 patients of CS, 4 patients (15.3%) were surgically upstaged. They received adjuvant chemotherapy. Among the remaining 22 patients who underwent CS in whom the stage remained same, 13 (50%) patients received chemotherapy because of their higher stage and 9 (35%) did not need any further treatment as the stage was 1A. Thus, chemotherapy could be avoided in 35% cases undergoing CS.

All three germ cell patients presented late with recurrence and so needed chemotherapy. Germ cell tumors are inadequately managed outside GOC. These patients are usually young. They should be counseled thoroughly to visit GOC for further management as early as possible with explanation that timely intervention might cure the cancer with preservation of fertility. In our study none of the cases attended GOC early due to ignorance and social reasons. As they presented with large recurrences, they were given NACT followed by IDS. This highlights the inadequacy of access to GOC for ovarian cancers in India.

Gynecologic oncologists have an essential role in treating women with gynecological cancer. Specialized physicians who work in multidisciplinary teams to treat women with gynecological cancers obtain the best clinical and oncological outcomes [18-20]. But even in countries with a high number of gynecologic oncologists, only minorities of women with gynecological cancer receive care by specialized physicians at referral institutions [21]. Thus from our study we offer following solutions: 1) Detailed preoperative investigations and triaging of suspicious adnexal masses should be done, 2) Patients with suspicious adnexal mass must be referred to gynaecologic oncologist or intraoperative assistance should be sought for, 3) Better referral practices which include timely referral, detailed operative notes and proper counseling of the patients, 4) Facility of frozen section must be made available, 5) Patients, especially young, must be educated regarding ovarian cancer and their management. They must be made aware regarding need of consulting gynaecologic oncologist and need of CSS, 6) Women must be empowered and educated to seek treatment early.

Conclusion

Our study has confirmed that among general gynaecologist and surgeons there is lack of suspicion of cancer in cases of suspicious ovarian mass which leads to inadequate preoperative workup. Thus, gynaecologic oncologist's consultation is rarely sought for. Such patients do not undergo comprehensive staging surgeries which lead to adverse outcomes. There is a need for proper referral practice and awareness of patients and gynaecologists regarding ovarian cancer and its preoperative evaluation.

Conflict of interest: None. **Disclaimer:** Nil.

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