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Prospective analysis of surgery for invasive and borderline tumors of ovary - lymph node ratio (A new concept)

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Abstract
Aim: The objective of this study was to analyse the surgical morbidity and mortality following the surgery for invasive and borderline ovarian tumors.
Materials and Methods: A prospective analysis of 54 patients who underwent surgery for borderline and invasive ovarian cancers in a single tertiary care centre during the period july 2013 to october 2016 was done.We analysed the surgical characteristics and tumor characteristics of the patient population studied.
Results: Invasive tumors were present in 42 patients (77.7%) and 12 patients(22.2%) had borderline tumors. Morbidity score - Clavien-Dindo classification grade I -6 patients(11.1%),grade II – 2 patients(3.7%),grade IIIA-1 patient(1.8%)and grade IVA-1 patient(1.8%).There was no postoperative mortality.
Conclusion: Lymph node ratio is a new concept in surgery for ovarian cancer. The prognostic significance of lymph node ratio would be known on the suvival analysis. Neoadjuvant chemotherapy facilitates optimal cytoreduction with reduced morbidity and mortality.

Keywords: Lymph node ratio, Clavien -Dindo classification, Lymphadenectomy, Neoadjuvant chemotherapy

Introduction

Approximately 200,000 women are diagnosed with ovarian cancer and 125,000 die each year worldwide [1]. Ovarian Cancer is the fifth leading cause of all cancer-related deaths in women [2]. Optimal cytoreductive surgery for ovarian cancer is performed either primarily or following neoadjuvant chemotherapy. The Gynecologic Oncology Group (GOG) has defined optimal debulking as residual implants less than 1 cm [3]. The use of neoadjuvant chemotherapy prior to cytoreductive surgery results in similar long term survival rates with lower post-operative morbidity and mortality in advanced ovarian cancer [4]. During debulking surgery and afterward, morbidity may be substantial [5]. Here we describe the prospective analysis of surgery for epithelial and borderline ovarian tumors including morbidity following the surgery.

Methods

A prospective analysis of 54 patients who underwent surgery for borderline and invasive ovarian cancers in a single tertiary care centre during the period july 2013 to october 2016 was done. The median age of the patients was 48 years (range 21-70 years). Co-morbid illness was present in 30 patients (55.5%). The average hemoglobin of the patients was 11.11gm% (range 9.2gm%-13. 4gm %). The average total White Blood cell count was 9223cells/c.mm (range 4100 cells/c. mm-20700 cells/ c.mm). The Average platelet count was 3.08Lakhs/c.mm (range 1.32lakh-4.61 lakh/c.mm).The Average upfront serum CA-125 was 785U/ml (range 6.9U/ ml-8043.5U/ml). Average post chemotherapy serum CA-125 was 57.8U/ml (range 7.3U/ml-388.5U/ml).25 patients (46.29%) underwent staging laporotomy for apparently early ovarian tumors by imaging and 29 patients (53.7%) underwent optimal interval cytoreduction following neoadjuvant chemotherapy for advanced disease. All patients with advanced disease received Taxol and Platinum based neoadujuvant chemotherapy. Bilateral Pelvic lymph node dissection was done in 45 patients(83.33%).Unilateral pelvic lymph node dissection was done in 5 young nulliparous patients(9.2%)as part of fertility sparing surgery with apparently early ovarian tumors. 15 patients(27.77%) underwent para-aortic lymph node dissection. Infracolic omentectomy was done in 44 patients (81.48%).10 patients (18.51%) with gross residual disease in the omentum underwent total omentectomy. The surgical characteristics of the patients are given in Table1.

Results

49 patients (90.74%) had epithelial ovarian tumors. of them, 38 patients(70.37%) had serous tumors,8 patients (14.81%) had mucinous tumors, 1 patient(1.8%) had endometroid tumor ,1 patient(1.8%) had undifferentiated carcinoma and 1 patient(1.8%) had combined serous papillary carcinoma and choriocarcinoma.1 patient(1.8%) had malignant germ cell tumour and 3 patients(5.5%) had granulosa cell tumors. Invasive tumors were present in 42 patients (77.7%) and 12 patients (22.2%) had borderline tumors. of the invasive tumors,12patients(28.5%) had GradeI,9 patients(21.4%) had Grade II and 21 patients(50%) had Grade III tumors.43 patients(79.62%) had unilateral tumors and 11 patients(20.37%) had bilateral tumors. Average nodal yield was 18 lymph nodes (range 5-47 lymph nodes).6 patients (13.33%) had pathologically positive lymph nodes. Lymph node ratio was of the range 0-20%(maximum range 80-100%) in 52 patients(96.29%).2 patients (4.4%) had Lymph node ratio in range 20-40%.Omentum was pathologically positive in 13 patients(24.07%).3 patients(10.34%) had pathologic complete response following neoadjuvant chemotherapy(Table2).

Stage distribution is as follows: Stage IA-17 patients (31.4%), IC2 – 1patient (1.8%), IC3-1patient (1.8%), stage II A-1patient (1.8%), stage IIB-3 patients (5.5%), stage IIIA2-1patient (1.8%), stage IIIC-28 patients (51.8%), stage IVA-2patients (3.7%). 9 patients (16.6%) developed recurrent disease on followup. Morbidity score - Clavien-Dindo classification grade I -6 patients (11.1%), grade II – 2 patients (3.7%), Grade IIIA-1 patient (1.8%) and grade IVA-1 patient (1.8%). There was no postoperative mortality. The Staging and Morbidity distribution are given in Table 3.

Table 1: Table showing the surgical characteristics of the patients.

Parameter	Number of patients(n)	percentage
Staging laporotomy	25	46.29%
Interval cytoreduction	29	53.7%
Bilateral pelvic lymph node dissection	45	83.33%
Unilateral pelvic lymph node dissection	5	9.2%
Para-aortic lymph node dissection	15	27.77%
Infracolic omentectomy	44	81.48%
Total omentectomy	10	18.51%

Table 2: Table showing the pathological characteristics of the patients.

Parameter	Number of patients(n)	Percentage (%)
Epithelial ovarian tumors	49	90.7%
Serous tumors	38	77.5%
Mucinous tumors	8	14.8%
Endometroid tumors	1	1.8%
Undifferentiated carcinoma	1	1.8%
Combined Serous papillary carcinoma and Choriocarcinoma	1	1.8%
Germ cell tumor	1	1.8%
Granulosa cell tumor	3	5.5.%
Invasive tumors	42	77.7%
Borderline Tumors	12	22.2%
Grade I	12	28.5%
Grade II	9	21.4%
Grade III	21	50%
Unilateral tumors	43	79.62%
Bilateral tumors	11	20.37%
Positive lymph nodes	6	13.33%
Lymph node ratio (0-20%)	52	96.29%
Lymph node ratio(20-40%)	2	4.4%
Omental positivity	13	24.07%
Pathological Complete Response	3	10.34%

Table 3: Table showing the staging and morbidity pattern of the patients

Parameter	Number of patients(n)	Percentage (%)
Stage		
IA	17	31.4%
IC2	1	1.8%
IC3	1	1.8%
IIA	1	1.8%
IIB	3	5.5.%
IIIA2	1	1.8%
IIIC	28	51.8%
IVA	2	3.7%
Clavien Dindo classification		
Grade I	6	11.1%
Grade II	2	3.7%
Grade IIIA	1	1.8%
Grade IVA	1	1.8%

Ddiscussion

Surgery is the mainstay in the treatment of epithelial ovarian cancer, and an extensive surgical staging is essential in the selection of most appropriate post-surgical therapy, requiring the removal of all macroscopic tumour, along with total abdominal hysterectomy, bilateral salpingo-oophorectomy, and infracolic omentectomy. Any ascitic fluid should be removed or, alternatively, peritoneal washing should be collected. Optimal staging includes (if disease appears confined to the ovary) biopsies of the diaphragmatic peritoneum, paracolic gutters, pelvic peritoneum, and sampling or dissection of paraortic and pelvic nodes [6]. Primary cytoreductive surgery followed by taxane-and platinum-based combination chemotherapy is the cornerstone of management for advanced ovarian cancer, and optimal cytoreduction is one of the most significant predictors of survival [7]. Some patients are too medically ill to initially undergo any type of abdominal operation, whereas others have disease that is obviously too extensive to be resected by an experienced ovarian cancer surgical team. Under these circumstances, neoadjuvant chemotherapy (NACT) is routinely used, usually after the diagnosis has been confirmed by paracentesis or CT-guided biopsy. The feasibility of surgery is reassessed after few courses of chemotherapy. In some series, NACT followed by interval debulking demonstrated comparable survival outcomes to those reported for primary surgery [8]. In our study, 25 patients (46.29%) underwent staging laporotomy for apparently early ovarian tumors and 29 patients (53.7%) underwent optimal interval cytoreduction following neoadjuvant chemotherapy for advanced disease.

Age appears to be an important factor. The association of a young age for a woman with an immune response capable of tackling and countering cells with mutations remains an important factor [9]. Studies by Smedley [10], Thigpen [11], and Duska [12] show age as a strong prognostic value. Increasing age is strongly associated with increased postoperative mortality following abdominal surgery [13]. The median age of patients in our study was 48 years (range 21-70 years).

Ørskov M, *et al*. found comorbidity (ASA>1) as a predictor of mortality at 0–180 days after surgery, and a decreasing importance over time [14]. Grann *et al*. [15] and Sperling *et al*. [16] also observed comorbidity to be a predictor of mortality. Data by Ørskov M, *et al*. may indicate that reduction of any pre-existing comorbidity could be important in the increasing survival after primary ovarian cancer surgery [14]. 30 patients (55.5%) had co-morbid illness in our series and it reflected on the Number of patients who underwent pelvic and paraortic lymph node dissections. In the setting of interval cytoreduction, paraaortic lymph node dissections and sometimes pelvic lymph node dissections were omitted as the patients could not withstand prolonged anaesthesia due to multiple co-morbidities.

There is a strong association between CA-125 at diagnosis and risk of relapse, in accordance with several epidemiologic studies on the association between CA-125 at diagnosis and survival from ovarian cancer [17, 18]. One study showed that, in serous ovarian tumors, the higher the CA-125 at diagnosis, the greater the likelihood of association with impaired disease-free and overall survival [19]. Retrospective studies reported strong association between the CA-125 level post chemotherapy and

prediction of progression-free survival and overall survival [20, 21]. In our series, the average CA-125 at diagnosis was 785U/ml (range 6.9 U/ml to 8043.5U/ml) and average post chemotherapy CA-125 was 57.8U/ml (range7.3 U/ml to 388.5U/ml).

Recent studies indicate that low-grade serous carcinoma has a significantly better prognosis than high-grade serous carcinoma [22, 23]. In advanced epithelial ovarian cancer, recent meta analyses report that the mucinous and clear-cell subtypes are associated with worse outcome [24, 25, 26, 27, 28]. In our study, 38 patients (77.5%) had serous tumours and 8 patients (16.32%) had mucinous tumours. One patient had combined serous papillary carcinoma and choriocarcinoma. In this patient, we reported the absence of choriocarcinoma in the ovarian primary with It's presence only in the peritoneal deposit first in the world literature [29]. Histologic subtype outperforms the tumor grade in prediction of survival, especially when combined with molecular markers [30]. Grade III tumors were predominant in our study in 21 patients (50%).

Lymphadenectomy plays a role in the treatment of ovarian cancer. It is of diagnostic value since tumors of apparently early stage show nodal involvement in about 20% to 40% of the cases [31] and are classified as stage IIIc. Lymphadenectomy may also have a therapeutic effect as retrospective studies comparing lymphadenectomy with no lymphadenectomy reported a survival benefit with this procedure [32, 33, 34]. The data on lymphadenectomy is conflicting, With one study showing that the patients with stage III disease (tumor residue >2 cm) that has been debulked sub optimally do not benefit from lymphadenectomy [35]. Other studies report no benefit even if the residual tumor size is smaller (1 cm) [36]. A prospective randomized trial showed that systematic lymphadenectomy did not result in better survival compared to selective lymphadenectomy [37]. Eoh KJ, *et al*. report that systematic lymph node dissection might have therapeutic value and improve prognosis for patients with optimally cytoreduced advanced ovarian cancer [39]. Mainly based on the retrospective findings current views on treating stage III disease suggest: systematic lymphadenectomy in cases of residual tumors <1 cm, nodal debulking only where tumors are larger than intra-abdominal residuals, and nodal sampling in stage IV disease with pleural effusions only [38]. To date, studies have not evaluated the impact of the number of lymph nodes harvested and lymph node ratio in ovarian cancer. The mean nodal yield following pelvic and paraaortic systematic nodal dissection in our cases was 18 lymph nodes. (Range 5-47).

Lymph node ratio defined as the ratio between total number of positive lymph nodes to the total number of lymph nodes harvested is a new concept in ovarian cancer. We have incorporated Lymph node ratio in our study .Lymph node ratio was of the range 20-40% (4.4%) in 2 patients. The range was 0-20% in rest of the patients.45 patients (83.33%) underwent bilateral pelvic lymph node dissection, 5 patients (9.2%) underwent unilateral pelvic lymph node dissection and 15 patients (27.77%) undewent para-aortic lymph node dissection.

Three-quarters of women who are newly diagnosed with invasive epithelial ovarian cancer present with stage III to IV disease (40).50.8% patients were stage III in a recent study by Ivana Rizzuto *et al.* on ROVAR score(41).Stage III patients were predominant in our study – 28 patients (51.8%) stage IIIC & 1 patient (1.8%) stage IIIA2.

The complication rate in a meta-analysis using population-based reports varied between 2.5% to 4.8% [42]. Single center studies displayed even lower complication rate around 2.5% which might not reflect the overall complication rate in a multicenter setting [42]. There are several bias to such reports including retrospective bias as well as reporting bias. Retrospective studies induce heterogeneity both in the population and treatment modalities. Arash Rafii *et al,* in a multicentre study, used the MSKCC scoring system to classify complications with overall rate of complications was 33% and 11% having severe complications [43]. In our study, only 2 patients (3.7%) had severe grade IIIA & IVA morbidity (Clavien-Dindo classification).

Our study being a prospective study, all the patients are on regular followup. At the end of followup, 9 patients (16.6%) have developed disease recurrences. 6 patients (11.11%) have died of the disease recurrence and 1 patient (1.8%) died of cardiac arrest. 3 patients (5.5%) are alive with disease recurrence on second line chemotherapy and supportive care.The prognostic significance of the various factors analysed would be known once the survival analysis is done at the end of the followup period.

Conclusion

Lymph node ratio is a new concept in surgery for ovarian cancer. The prognostic significance of lymph node ratio would be known on the survival analysis. Neoadjuvant chemotherapy facilitates optimal cytoreduction with reduced morbidity and mortality. Meticulous surgery with aggressive postoperative care would help reduce the morbidity & mortality in patients undergoing surgery for ovarian cancer.

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Disclosure of Interests
There are no specific financial, personal, political, intellectual or religious interests.

Authorship
Dr. Sivasundari Maharajan was actively involved in the collection of the data and early processing of the data. Dr. Shanmugasundaram compiled all the data, Analysed and made the final format of the article.

Ethics approval
Informed written consent was obtained from all the patients as part of surgical consent.

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