Management of Epithelial Ovarian Cancer at A Tertiary Centre In South Africa: A Retrospective Evaluation of Early Recurrence and Contributory Factors

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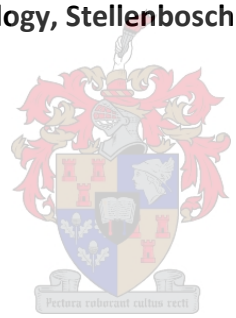

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DECLARATION

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Yours Truly,

Author's signature…….

DEDICATION

To God forever be the glory for this achievement.

To my dear wife and children for their sacrifice for two years to allow me to pursue this dream.

ACKNOWLEDGEMENT

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ABSTRACT

Introduction. Epithelial ovarian cancer is associated with high recurrence rates and poor survival, especially if the disease is advanced, surgery sub-optimal, and or has high-grade histology. However, there is a paucity of information regarding recurrence and survival in epithelial ovarian cancer in Africa. We aimed to assess early recurrence rate, associated factors, and patterns of recurrence of epithelial ovarian cancer, at a tertiary centre in South Africa.

Materials and Methods. A retrospective review of records of patients with epithelial ovarian cancer managed in a single institution over a nine-year period was performed with relevant ethics approval (S18/04/078). Case records were searched and information about age, parity, baseline serum CA125, histologic sub-type and grade, FIGO stage, neoadjuvant and adjuvant chemotherapy status and number of cycles, optimality of staging/debulking surgery, the month adjuvant treatment was completed, and month of recurrence were abstracted. Exclusion criteria included documented primary peritoneal cancer, platinum-resistant patients, and those with inadequate follow-up information. IBM SPSS version 25® was used for statistical analysis. Descriptive statistics which included percentages, means and medians, were used to assess recurrence. Fisher's exact and χ^2 tests were used to assess for factors with significant association to early recurrence. p-value<0.05 was considered statistically significant.

Results. A total of 124 patients definitively treated for epithelial ovarian cancer with adequate records were identified. Final analysis was performed for 91 patients after 33 were excluded. Early-stage disease comprised 47% of the cases. Nearly 50% of patients had papillary serous histology. Optimal cytoreduction was achieved in 70% of cases. Recurrence rate ≤ 24 months was 33% with a median time to recurrence of 14 months (IQR 8.75-20.75) for stages I and II disease, and 67% with a median time to recurrence of 12 months (IQR 8-14.25) for stages III and IV disease. Isolated pelvic recurrence was diagnosed in 50% of early- stage disease but, a trend towards multiple distant-site recurrence was observed in FIGO stage III/IV disease. Tumour histology was the only significant factor associated with early recurrence (p=0.005). Cytoreduction status, use of neoadjuvant chemotherapy, baseline CA125, parity, and patient age did not demonstrate association with early recurrence. *Conclusions.* Early recurrence of epithelial ovarian cancer in this patient population appears higher compared to published literature. However, a standardized surgical protocol, objective intra-operative assessment of residual tumour, and adequate surgical record are essential for an in-depth study of surgical factors in ovarian cancer recurrence for our setting.

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LIST OF ACRONYMS

ACT	Adjuvant Chemotherapy
AGO	Arbeitsgemeinschaft Gynaekologische Onkologie
CA125	Carcinoma Antigen 125
CRS	Cytoreductive Surgery
EOC	Epithelial Ovarian Cancer
FIGO	International Federation of Gynecology and Obstetrics
HREC	Health and Research Ethics Committee
ICU	Intensive Care Unit
IDS	Interval Debulking Surgery
NACT	Neo-Adjuvant Chemotherapy
PARP	Poly (ADP) Ribose Polymerase
PDS	Primary Debulking Surgery
RFI	Recurrence Free Interval
TAHBSO	Total Abdominal Hysterectomy and Bilateral Salpingo-Oophorectomy

OPERATIONAL DEFINITIONS

"Recurrence" was defined as documented new imaging abnormality, deterioration of clinical picture, and/or raised serum CA 125 twice the normal post-treatment value, and/or new positive histo/cyto-pathologic report at least six months after completion of adjuvant chemotherapy.

"Early recurrence" was defined as occurrence of disease under two years of completion of adjuvant therapy.

"Recurrence-Free Interval'' (RFI) was defined as the duration in months, from completing adjuvant chemotherapy to first recurrence of disease.

"Patterns of recurrence" implied disease distribution at recurrence

"Definitive treatment" was considered as a combination of surgery (at least TAH+ BSO + omentectomy) followed by ≥ three cycles of adjuvant chemotherapy, or surgery alone for FIGO stage IA/B grade 1 disease.

"Adequate surgical staging" was defined as cytologic evaluation of ascitic fluid, peritoneal biopsies, total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymphadenectomy in patients with disease clinically confined to the pelvis.

"Optimal debulking surgery" was defined as total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy and tumour debulking to ≤ 1.0 cm of residual disease.

"Ultra-radical surgery" included multiple bowel resections, splenectomy, and or peritoneal/diaphragmatic stripping.

"Early-stage disease" was collectively considered as stages I and II disease, while high-risk early-stage disease comprised stages IA/B with grade 2-3 histology, IC, and IIA/B regardless of tumour grade.

"Advanced-stage disease" included both FIGO stages III and IV.

Type I epithelial ovarian cancer includes clear-cell, mucinous, endometrioid and low-grade serous histologies.

Type II tumours include high-grade serous, mixed epithelial -stromal and undifferentiated carcinoma.

CHAPTER ONE: INTRODUCTION

1.1 Background

The five-year survival after diagnosis of EOC is generally around 30% in contrast to other gynecologic malignancies, and across the globe there is wide disparity in survival with majority of the developing world having much lower survival figures (1,2).

The standard management of EOC is optimal staging/primary debulking surgery (PDS) followed by three to six cycles of timely adjuvant chemotherapy (ACT) (3–7). When disease is clinically confined to the pelvis, para-aortic and pelvic lymphadenectomy upstages one-third of patients, but its impact on prognosis is still debatable (8–10).

Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) in patients with advanced disease and high-tumour load (HTL) is an acceptable alternative to PDS to minimize surgical morbidity without compromising survival (11–13).

The objective of surgery regardless of approach is to resect all macroscopic tumour or at a minimum achieve residual tumour ≤ 1cm as residual disease volume inversely correlates with survival (14). While optimal surgical effort is the cornerstone of EOC treatment, other patient and tumour-related factors potentially influence surgical and survival outcomes.

The impact of adjuvant chemotherapy regime on recurrence and survival was established two decades ago. Combination of platinum and paclitaxel results in superior recurrence-free and overall survival compared to platinum and cyclophosphamide particularly when debulking surgery is sub-optimal (15).

At Tygerberg Hospital, pelvic and paraaortic lymphadenectomy, a component of standard staging surgery is not routine. Rather, patients with high-risk stage I and stage II EOC receive three to six cycles of single-agent carboplatin or carboplatin in combination with paclitaxel or cyclophosphamide: the latter being the most commonly used combination until recently. To minimize the need for ultra-radical surgery, patients with advanced-stage disease with clinical and radiologic HTL undergo IDS three weeks after last NACT cycle. The justification for these approaches is limited theatre time and ICU support services. Anecdotal information however, suggests that optimal surgery rate for EOC at our institution may be modest regardless of approach.

1.2 Problem statement

Recurrence after treatment of EOC at Tygerberg hospital is not well documented.

1.3 Justification

Early recurrence in ovarian cancer is in part a reflection of the adequacy of surgery performed. This study would determine the need for generation of a surgical protocol to obtain maximum surgical benefit in a modestly resourced setting. It would also provide information to future investigators interested in epithelial ovarian cancer survival for the South African population.

1.4 Outcomes of the study

1.4.1 Primary outcome

The recurrence rate at 24 months among patients managed for EOC.

1.4.2 Secondary outcomes

1. Contributing factors to early recurrence
2. Patterns of disease recurrence

CHAPTER TWO: LITERATURE REVIEW

2.1 Epidemiology of epithelial ovarian cancer

Epithelial ovarian cancer (EOC) constitutes more than two-thirds of the ovarian cancer (OC) burden with a mean age at diagnosis of 58 and 64 years for types I and II tumours respectively (2). High-grade serous (HGS) carcinoma is the most prevalent and often presents with advanced-stage disease (16,17).

The five-year survival for FIGO stages IA, IB, IC, II, IIIA, IIIB, IIIC and IV EOC is 89.6%, 86.1%, 83.4%, 70.7%, 46.7%, 41.5%, 32.5% , and 18.6% respectively (18). Generally, survival for all stages of OC has modestly improved from 29% in the 1970s to 39% in 2006, in part due to improvements in surgical care and chemotherapy (1,18). However, there still remains wide disparity in survival with inferior outcomes observed in the developing world. (1,2,19). Survival data for ovarian cancer in Sub-Saharan Africa is disappointingly very scanty.

2.2 Disease recurrence and prognostic factors

Recurrence after primary treatment for high-risk early and advanced EOC is often the rule. The median recurrence-free interval (RFI) for high-risk early-stage disease is 21 months, and although early-stage disease has a good prognosis, the median overall survival after recurrence is poor and comparable to recurrent advanced-stage disease (20).

Data from multiple cohorts indicate that residual tumour size after debulking surgery is a critical factor in determining recurrence-free survival (RFS) in advanced-stage disease (21). Patients who are optimally treated achieve 38 months of RFS compared to 10 months for those with sub-optimal residual disease (14). Furthermore, there is a 5.5% increment in median overall survival for every 10% of that cohort who attain complete debulking (22).

The FIGO stage and tumour burden are influenced by patient age, histologic sub-type and tumour grade. Age over 60 years, HGS carcinoma and other poorly-differentiated epithelial sub-types are associated with advanced disease and high-tumour burden (23,24). HTL is an independent poor prognostic factor and probably a reflection of an inherent aggressive tumour behavior (25).

HGS carcinoma demonstrates a higher response to platinum-based chemotherapy than clear-cell and mucinous variants (5). In addition to affecting platinum sensitivity, tumour grade influences recurrence patterns with high-grade disease often recurring in distant sites irrespective of FIGO stage of disease (26).

A correlation between tumour biology and CA125 levels has been observed. High serum CA125 level is associated with wide spread metastatic disease, a common occurrence with poorly differentiated tumours (27). But, the surgical utility of serum CA125 level is not well established, and various cutoffs that have been set to predict optimal PDS have low positive predictive value (PPV) (28,29). Conversely, post-NACT serum CA125 level appears to accurately predict complete IDS but this has not been validated (30,31).

The impact of gene mutations in EOC is an emerging field. It is estimated that about 15% of women with non-mucinous, but predominantly HGS have a BRCA gene mutation (32). BRCA mutations have been reported by some authors to confer superior survival compared to sporadic variants, partly due to increased platinum sensitivity and utility of PARP inhibitors (33). A recent study indicates that nearly one-fourth of all EOC patients carry a homologous recombination deficiency (HRD) gene with observed superior survival in contrast to non-HRD patients (34). However, high levels of PARP, FANCD2 and or P53, are associated with a cumulative first year cancer incidence of 17% and high platinum resistance, in contrast with tumours that express PTEN, H2AX and ATM (35). Limited published data indicate that BRCA mutations are uncommon in the South African black population (36). But the level of non-BRCA HRD in this population is also not established.

Attempts have been made to stratify patients into low, intermediate, and high risk of recurrence based on FIGO stage, histologic sub-type and grade, baseline and post-adjuvant chemotherapy serum CA125 level, residual disease status after debulking surgery, and post-adjuvant chemotherapy (37). Validation of such a prognostic score would help to tailor follow-up and utilize resources rationally.

2.3 Primary management of Epithelial Ovarian Cancer

The standard treatment of EOC is upfront staging/debulking surgery to achieve largest residual tumour of less than 1 cm, followed by timely adjuvant platinum and taxane-based chemotherapy (6,15). Optimally-staged IA and IB grade 1 disease does not require adjuvant chemotherapy (3).

Patients with disease confined to the pelvis undergo a full staging operation inclusive of para-aortic (up to renal vessels) and pelvic lymph node dissection (6,38). This is due to the fact that 37% of patients with apparent early-stage EOC will be up-staged on the basis of occult retroperitoneal lymph node metastases (8), and this has an impact on adjuvant chemotherapy and prognosis. Some schools of thought have questioned the need for extensive lymphadenectomy as this has no bearing on survival, and high-risk stage I and II disease is, nonetheless treated with adjuvant chemotherapy

(10,39). The setback of this strategy is that nearly one-third of patients who are considered to have early-stage disease actually have stage III disease (40), and their survival is inferior to actual stage I and II patients.

In advanced EOC, optimal debulking surgery offers improved survival outcomes (6,41). Due to the disease's propensity for parietal and visceral peritoneal spread to the abdominal cavity, radical, and or ultra-radical surgery is commonly required to achieve optimal/maximal cytoreduction with attendant severe morbidity and mortality of 5% (42–45). This has led to exploration of the role of NACT in patients with HTL. Randomized trials have shown that NACT followed by IDS in this category of patients offers better intra-operative and immediate post-operative outcomes compared to PDS (7,12,46). The proportion of optimal residual disease rate after NACT has been shown to be higher than after PDS, but the median overall survival was comparatively lower (11,41,46). Multi-visceral resection in IDS to achieve optimal/maximal cytoreduction does not translate into improved survival (25). Reduced impact of NACT on median overall survival may be related to inherent aggressive tumour biology and under-estimation of residual disease after IDS (25,47). Nevertheless, the benefits related to reduced intra-operative and immediate post-operative morbidity have made IDS an increasingly common approach for patients with HTL EOC in some European centres and the developing world (6,7,38). The value of IDS approach in HTL advanced EOC has brought forth triage laparoscopy to reduce futile PDS, a practice that has gained acceptance in some centres (6,48).

It has been observed that optimality of surgery is influenced by level of training of the surgeon. Staging surgery performed by general gynecologists is commonly sub-optimal and associated with inferior survival in contrast to trained gynecologic oncologists (49,50). Optimal debulking rates correlate with patient volume as demonstrated by 70-90% optimal cytoreduction rates in some specialized high-volume centers in the developed world (51).

2.4 management of epithelial ovarian cancer: A South African perspective

The public oncology services, especially in the Western Cape Province, are centralized to tertiary centres. However, sub-optimal surgery for ovarian cancer by general gynecologists is not unusual. Triage laparoscopy in advanced-stage disease is not yet common practice in most tertiary institutions, but NACT followed by IDS is a common approach for advanced-stage disease in the public setting.

A 2014 survey indicated that most gynecologic oncologists in South Africa achieved optimal cytoreduction in over 60% of cases of ovarian cancer. Nonetheless, more than 50% of them reported

a lack of expertise in upper abdominal procedures (52). A paucity of published data on ovarian cancer management and outcomes in South Africa hinders substantiation of these observations.

2.5 Management of recurrent ovarian cancer

It is well established that repeat use of carboplatin and paclitaxel for platinum-sensitive disease yields a superior median survival of 33 months with acceptable toxicity compared to other combinations (53). Additionally, the benefit of targeted agents in combination with chemotherapy and as maintenance therapy in platinum-sensitive disease is established (54–57).

However, the utility of surgery in the management of recurrent disease is still uncertain. A role for secondary CRS in select patients has been observed and institutions use various validated criteria: AGO OVAR, Tian, and Memorial Sloan Kettering Cancer Centre criteria. Notably, RFI is the common denominator to determine probability of achieving no gross residual status in secondary CRS (58–60).

CHAPTER THREE: METHODOLOGY

3.1 Study design

This was a retrospective review of patient records.

3.2 Patient population and setting

Patients definitively treated for EOC during the years 2006 to 2014 at the Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Tygerberg Hospital (TBH). TBH is one of two tertiary hospitals in the Western Cape Province of South Africa.

3.3 Inclusion criteria

Included all patients with documented EOC or Fallopian-tube cancer who underwent went definitive treatment.

3.4 Exclusion criteria

Borderline tumours, primary peritoneal cancer, uncertain histologic diagnosis, recurrence or progression under six months of completing ACT, fertility-sparing treatment, those who had less than three cycles of ACT, or had insufficient clinical information were excluded.

3.5 Ethics Approval

Ethics approval (S18/04/078) was obtained from the Health and Research Ethics Committee (HREC) of Stellenbosch University prior to commencement of the study.

3.6 Data Collection

All files of patients with an ovarian cancer diagnosis managed between January 2006 and December 2014 were retrieved from the database of the gynecologic oncology unit. Those with a pathologic diagnosis of EOC/fallopian tube cancer were selected. The electronic database was searched to add relevant missing information. The treatment administered was then evaluated to identify those who met the inclusion criteria.

Data collection consisted of patient age at diagnosis, parity, baseline serum CA125 level, FIGO stage, histologic sub-type and grade, NACT and number of treatment cycles, date of operation and residual tumour status, ACT and number of treatment cycles, date of completion of ACT, recurrence status, and date when diagnosis of recurrence was made, were abstracted.

The surgical notes and pathology data were assessed to determine whether CRS and/or surgical staging was optimal. The sites of recurrence were recorded as per case notes. All FIGO stage IC

pathology reports were harmonized to reflect the FIGO 2014 staging format. Recurrence-free interval (RFI) was estimated for each patient based on the month the patient completed ACT or had surgery alone-where ACT was not indicated, and the time of documented recurrence. Race was difficult to capture so it was ignored.

Each patient file was given a unique ID consisting of a serial number and the year of treatment. The database was password-protected and accessible only to the principal investigator on a personal computer to ensure confidentiality.

3.7 Data Analysis

The data were converted to Microsoft excel 2010 format and cleaned for completeness before exportation to IBM SPSS version 25® for analysis. Descriptive statistics were used to analyze the data. The following variables were evaluated: patient age, parity, baseline CA125, FIGO stage, histologic sub-type and grade, NACT, degree of CRS and ACT. The outcomes of interest were two-year recurrence rate, and sites of recurrence.

Median with inter-quartile range (IQR 25^{th} to 75^{th} percentiles), mean with standard deviation, and counts expressed as percentages, were computed to describe the continuous and categorical variables respectively. Differences in variables between patients with and without recurrence within twenty-four months were assessed using the Pearson's chi-square and Fisher's exact tests. Association was considered statistically significant if p-value was <0.05.

CHAPTER FOUR: RESULTS

4.1 Description of Baseline data

In the hospital database, 200 patient records over a nine-year period were identified with an ovarian cancer diagnosis. A total of 124 EOC patients who received definitive treatment between January 2006 and December 2014, were selected. Excluded patients were 33 (27%): 29 (88%) patients had platinum- resistant/refractory disease, and four (12%) patients had insufficient follow-up information. Of the patients with platinum-resistant or refractory disease, 22 (76%) and seven (24%) had advanced and early-stage disease respectively. A total of 91 patients were available for final analysis. Of these, 47% (43/91) and 53% (48/91) patients had early and advanced-stage disease respectively. In nearly 50% of patients we could not trace a record of the baseline CA125 results. Parity was unknown for four patents. Among stage IC patients, eight (44%) patients had FIGO IC1, five (28%) FIGO IC2, and five (28%) FIGO IC3 disease. Among stage IV patients, nearly 70% had stage IVB disease. Details of FIGO stage II and III patients are as indicted in Table 1 respectively.

Tumour grade for endometrioid and mucinous histologies was not explicit in many reports. Twelve patients had combinations of mixed histology and were grouped as such for simplicity. Only two patients had a BRCA test performed and documented prior to 2014. The reason was that BRCA testing was not yet routine practice.

Only nine percent (4/43) of patients with early-stage disease had an optimal staging operation which included some form of retroperitoneal lymph node assessment (only one patient had both pelvic and para-aortic nodal assessment), peritoneal biopsies and sampling of the hemidiaphragms. Peritoneal biopsy was performed randomly in 40% (15/39) of patients without diaphragmatic sampling.

Most of the surgical notes did not indicate the site and size of residual tumour, but there was written indication whether tumour debulking was optimal or not. In cases where it was not documented, we analyzed the operative findings and the ease or difficulty with which the operation was done to determine whether cytoreduction was optimal. Some form of bowel resection (mainly rectosigmoid) during PDS/IDS was performed in less than 10% of the patients. No patient had documented peritoneal stripping or splenectomy.

NACT was considered as at least two cycles of chemotherapy received either as single-agent or in combination before surgery. Of the patients with advanced disease, 39.6% (19/48) received NACT and 42% (8/19) of them were documented as optimally cytoreduced. Nearly 90% the patients who

got NACT received carboplatin and cyclophosphamide as paclitaxel was not readily available prior to 2014.

ACT was not administered to 19% (17/91) of the patients due to low-risk disease. On average, six cycles of ACT were administered to eligible patients. Those who received carboplatin/cyclophosphamide, carboplatin/Taxol and single-agent carboplatin were 55%, 12% and 11% respectively. In 15% (11/74) of the patients we could not ascertain the ACT regimen they received (data not shown in the tables).

Sites of recurrence were taken as per case notes and documented imaging results which included mainly ultrasound and chest radiography. Computed tomography was not used often to assess extent of disease recurrence among patients who recurred within twelve months as they were considered non-surgical candidates.

Table 4.1: Clinical and pathologic characteristics (N=91)

Characteristics		No. of patients	(%)
Mean-Age (years) (SD)	56±12		
Median-CA125 (IQR)	522.4 (86.6-1257)	47	51.6
Missing CA-125		44	48.4
Parity:			
0		20	22.0
1-2		28	30.8
≥3		39	42.8
Missing		4	4.4
FIGO[a] stage:			
IA+IB		15	16.4
IC		20	22.0
IIA+IIB		2	2.2
IIC		6	6.6
IIIA		4	4.4
IIIB		5	5.5
IIIC		26	28.6
IV		13	14.3
Histology			
Papillary Serous		42	46.1
Low-grade Serous		9	9.9
Clear Cell		4	4.4
Endometrioid		13	14.3
Mucinous		11	12.1
Others*		12	13.2
Cytoreductive surgery:			
Optimal		64	70.3
Sub-optimal		16	17.6
Not certain		11	12.1
Surgical Staging:			
Optimal		4	9.3
Sub-optimal		39	90.7
NACT∗:			
Yes		19	39.6
No		28	58.3
Not certain		1	2.1
IDS[b] (Stage III IV):			
Optimal		8	42.1
Sub-optimal		9	47.4
Not certain		2	10.5
PDS[d] (Stage III-IV):			
Optimal			
Sub-optimal		13	46.4
Not certain		9	32.2
		6	21.4
Adjuvant chemotherapy:			
Yes		74	81.3
No		17	18.7

[a] International Federation of Gynecology and Obstetrics; [b] Interval Debulking Surgery, [d] Primary Debulking Surgery; * Mixed and rare histologies; ∗Neoadjuvant chemotherapy

4.2 Recurrence data

The median time of follow-up was 22 months (IQR 12-58.5 months). There was high loss to follow-up by the 24th month and vital status was difficult to ascertain. Patients who completed at least 24 months of follow-up without documented recurrence were considered as such. Conversely, those who were lost to follow-up prior to 24 months were considered to have had a recurrence unless other cause of death was clearly documented in the hospital database.

Among patients with disease grossly limited to the pelvis who recurred within 24 months, 14% were stage IA/IB, 57% stage IC, and 29% stage II.

The combined median RFI was 12 months (IQR 8-16). Recurrence in early-stage disease occurred in the pelvis in half of patients. FIGO stage III/IV disease displayed a tendency towards multiple and distant-site recurrence.

Table 4.2: 24-months recurrence by stage and site

Characteristics	FIGO I&II	FIGO III&IV
Recurrence, n (%)		
Yes	14 (32.6)	32 (66.7)
No	29 (67.4)	16 (33.3)
RFI, n (%)		
≤12 months	7 (50)	20 (62.5)
13-24 months	7 (50)	12 (37.5)
Median RFI* (IQR)	14 (8.75-20.75)	12 (8-14.25)
Site of Recurrence, n (%)		
Pelvis only	9 (60)	8 (25)
Pelvis and Abdomen	3 (20)	9 (28.1)
Distant site(s)	3 (20)	11 (34.4)
*Site not defined***	-	4 (12.5)

* Recurrence Free Interval in months; ∗ Interval Debulking Surgery; ** Recurrence documented by evidence of rising CA125 and clinical deterioration.

4.3 Contributory factors to early recurrence

Histology showed a strong association with two-year recurrence. Patient age, Parity, Optimal debulking/staging, serum CA125 and NACT did not demonstrate association.

Table 4.3: Clinicopathologic factors and 24-months recurrence

Factor	Recurred ≤24months (N=46) n (%)	No Recurrence (N=45) n (%)	p-value
Age (years)			
≤59	25 (54.3)	30 (66.7)	0.551
≥60	21 (45.7)	15 (33.3)	
Parity			
0	11 (23.9)	8 (17.8)	0.245
1-2	13 (28.3)	15 (33.3)	
≥3	20 (43.5)	18 (40)	
Not certain	2(4.3)	4(10)	
Baseline CA125 (U/ML)			
≤500	7 (15.2)	16 (35.6)	0.241
≥501	14 (30.4)	9 (20)	
Missing	25 (54.4)	20 (44.4)	
Histology			
Papillary Serous	25 (54.4)	17 (37.8)	0.005
Low-grade Serous	7 (15.2)	2 (4.4)	
Clear Cell	2 (4.3)	2 (4.4)	
Endometroid	4 (8.7)	9 (20)	
Mucinous	4 (8.7)	7 (15.6)	
Others	4 (8.7)	8 (17.8)	
NACT*			
Yes	14 (30.4)	5 (11.1)	0.512
No	32 (69.6)	40 (88.9)	
Surgical Staging			
Optimal	3 (14.3)	1 (4.5)	0.473
Sub-optimal	18 (85.7)	21 (95.5)	
CRS[e]			
Optimal	25 (54.4)	39 (86.7)	1.000
Sub-optimal	14 (30.4)	2 (4.4)	
Not certain	7 (15.2)	4 (8.9)	

CHAPTER FIVE: DISCUSSION

This retrospective single-institution study aimed to assess two-year recurrence rate, determine patterns of recurrence, and identify potential contributors to early recurrence. Of the 91 eligible women treated for EOC, 50% had disease recurrence within 24 months of completion of therapy. The two-year recurrence rate was 33% and 67% for early and advanced-stage disease respectively. The median time to recurrence was 12 months (IQR 8-16) without a statistical difference between the two groups. Tumour histology was the sole factor that demonstrated association with early recurrence with p-value=0.005. Adequacy of surgical staging or debulking, baseline serum CA125 level, NACT, patient age, and parity did not demonstrate association.

American and European studies have demonstrated that 25-30% of patients treated for early- stage disease will develop a recurrence within five years (26,40,61). A study by Chan et al. indicated a median time to recurrence of 21 months among patients treated for early-stage epithelial ovarian cancer after a median follow up time of 5 years (20). A 33% recurrence rate within 24 months for early-stage disease in our study is comparatively high. This may be attributable to under-staging of a significant number of patients with presumed early-stage disease. This is plausible as patients with early-stage disease comprised 47% of our study cohort compared to 30% in other published studies (62,63), as well as absence of statistical difference in RFI between early and advanced-stage disease patients who developed early recurrence. Available evidence indicates that about one-third of patients with clinical stage I/II disease in reality have stage III disease after performing pelvic and para-aortic lymphadenectomy (8), a procedure that was not part of routine staging surgery for our patients. However, a correlation between sub-optimal surgical staging and early recurrence was not observed in our study. With a paltry 9% of patients undergoing optimal staging surgery, its impact on early recurrence cannot be excluded. It is also noteworthy that 40% of eligible patients had random peritoneal biopsies performed as part of staging, but none were up-staged, confirming an established fact that random peritoneal biopsies do not result in improved detection of microscopic peritoneal disease (64).

A multi-institutional French study retrospectively evaluated 500 patients with advanced EOC, fallopian tube, and primary peritoneal cancer and showed that 26% (inclusive of platinum-resistant patients) recurred within 12 months after completion of treatment, and a further 52% recurred within 36 months with a median follow up of 49 months. Complete cytoreduction was achieved in 70% of patients and two-thirds of their cohort received NACT (65). In the study by Gadducci and colleagues, 30% of all optimally cytoreduced patients with advanced-disease recurred within 12

months (66). In our study, a recurrence rate of 68% within 24 months in advanced-stage-disease, after exclusion of platinum-resistant/refractory patients, is significantly higher than the aforementioned figures albeit with a 70% optimal cytoreduction rate comparable to Vidal et al. (65). This could be due to significant under-estimation of intra-operative residual disease volume resulting in a falsely high optimally-cytoreduced proportion of patients with consequent high early-recurrence rate: an observation that augments a known fact that optimal/complete cytoreduction is associated with longer recurrence-free survival (51,67). Eskander and co-workers showed that there was poor correlation between attending surgeon's estimate of residual tumour and post-operative computed tomography (CT) scan findings (68). Optimal staging and documentation of size and site of residual disease rates for our cohort fell very short of established quality indicators (95% and 90% respectively) for OC surgery (69), potentially masking the expected effect of cytoreductive surgery on RFI.

Our study did not demonstrate a negative effect of NACT on early recurrence. Several studies have shown that survival outcomes between neoadjuvant chemotherapy followed by IDS are comparable to PDS in patients with advanced EOC (11,46). Although patients who had NACT were more likely to have optimal cytoreduction, other studies indicate they were likely to recur earlier and had inferior survival compared to their counterparts who underwent optimal/complete PDS (66,70). A study in Finland demonstrated that peri-operative visual estimation of residual disease during IDS is less sensitive compared to PDS potentially leading to under-estimation of residual disease (47). However, small numbers of patients who were given NACT in our cohort preclude a definitive conclusion on this subject.

The effect of baseline serum CA125 level on early recurrence was not demonstrable. Chi et al. demonstrated that baseline serum CA 125 ≥ 500U/ predicted optimal cytoreduction: a factor that correlates with RFI, with a sensitivity of 78%, specificity of 73%, positive predictive value of 78%, and negative predictive value of 73% (29). Contrastingly, Memarzadeh et al. failed to confirm this finding albeit with higher CA 125 cut-offs (28). Our finding appears to agree with the latter's observation.

Patient age and parity did not demonstrate association with early recurrence. A Gynecologic Oncology Group study however, showed that patients over 60 years of age with early-stage disease had higher recurrence and poorer survival compared to their younger counterparts (26). Small patient numbers and aggregation of low and high-grade histology which are epidemiologically distinct entities (23) potentially masked the effect of age on early recurrence. Bodelon and

colleagues observed that parity had not effect on recurrence (71), an observation our finding reaffirms. Although pregnancy reduces the risk of EOC, it does not seem to have a bearing on tumour biology (72).

Our study demonstrates the already known association between tumour histology and early recurrence (2,73). However, few patients with non-serous histologies could not enable sub-group assessment for potential differences in recurrence rates and patterns of recurrence among early-stage high-grade serous, clear-cell and mucinous carcinomas. Nevertheless, available evidence demonstrates that there is no difference in recurrence between clear cell and high-grade serous tumours (74).

Regarding patterns of recurrence, isolated pelvic recurrence was diagnosed in 60% of the patients treated for early-stage disease. This is supported by Trimbos et al. who demonstrated similar results (40). Patients with advanced disease showed a logical tendency towards distant multiple site recurrence. Singh et al. observed similar results with a higher predisposition for multiple distant-site metastases among African American patients (75). We did not capture race for our cohort to determine if differences in recurrence patterns exist among racial groups, nevertheless our institution serves a predominantly black population. The minimal use of computed tomography imaging for patients who recurred under 12 months and its low sensitivity however potentially under-estimates upper abdominal and retroperitoneal recurrence in our study.

The strengths of this study include a well-kept and legible database with access to pathologic reports that assured accurate histology information. Patients were managed by a multi-disciplinary team inclusive of trained gynaecologic oncology surgeons, medical oncologists, experienced pathologists and radiologists ensuring optimum management for epithelial ovarian cancer in a modest resource setting.

The weaknesses of the study include the inherent bias of retrospective observational studies, subjective nature of retrospective evaluation of surgical notes to determine intra-operative residual tumour status in some cases, and inability to establish vital status of many patients due to limited scope of the ethics approval.

Conclusions

One in three patients treated for early-stage epithelial ovarian cancer and two-thirds of those with advanced-stage disease recurred within 24 months with a median interval to recurrence of 12 months. These recurrence figures are higher in comparison to Western published literature.

The rates of optimal staging and documentation of size and site of residual tumour in our cohort fall very short of established quality indicators for ovarian cancer surgery. There appears to be significant under-estimation of intra-operative residual disease.

Due to small patient numbers, however, we were unable to ascertain the impact of different chemotherapy combinations and histologic sub-types on early recurrence for this cohort.

Recommendations

A standardized protocol for ovarian cancer surgery and systematic documentation are required to assure adherence to established quality indicators and homogenize documentation among surgeons.

An objective intra-operative method of assessment of residual disease should replace visual estimation to improve assessment of survival outcomes.

An extended study to determine survival of this cohort to further inform current management practices is warranted.

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