# Quality of life following surgery in advanced ovarian cancer

by

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# ABSTRACT

Research presented in this thesis was driven by the need to inform our current knowledge on Quality of life (QoL) of patients undergoing extensive surgery for advanced ovarian cancer. National Institute for Health and Care Excellence (NICE) commissioned this multicentre prospective observational research to update Interventional Procedure Guideline. Existing evidence supports the utilisation of extensive surgery to achieve complete debulking to improve survival outcomes. The systematic review found no good quality studies to inform QoL outcomes for extensive surgery. The observational study showed significant variation in case selection and surgical intervention across participating centres and patients undergoing extensive surgeries did not report a worse QoL compared to patients having less extensive surgeries. A specific investigation into incidence of acute kidney injury (AKI) as a parallel project showed overall incidence of AKI during treatment of advanced ovarian cancer is high (30%), however, most of these incidences were transient, related to patient's pre-existing co-morbidities and did not cause major deleterious effect on health within the study period. The result will inform the policy makers, organisations, clinicians and patients and should reassure them regarding use of extensive surgery in advanced ovarian cancer.

# DEDICATION

This thesis is dedicated to the memory of my late grandfather Sri Ram Balak Singh, who had an immense confidence in my ability, my mother Subhadra Devi and father Sri Chandra Kumar Singh who supported me throughout my career in making all the decisions. I thank you all for your unconditional love and support.

Late Sri Ram Balak Singh (1909 – 2003)

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All principal investigators, research nurses, and trainees, having to put up with my request to provide data and collaborate in the study.

And last but never the least, I owe a huge amount of thanks to my wife Zainab. Thank you for all your support over the years and encouraging me to achieve my true potential. A kind thanks and love for my children “Ishan” and “Muskaan” for understanding and allowing me to work over evenings and weekends.

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# ABBREVIATIONS

| | |
|---|---|
| ACCI: | Age-adjusted Charlson's comorbidity index |
| AKI: | Acute kidney injury |
| AKIN: | Acute Kidney Injury Network |
| ANOVA: | Analysis of Variance |
| ASA | American Society of Anaesthesiologists |
| BMI: | Body mass index |
| CCI: | Charlson's comorbidity index |
| CHORUS: | Chemotherapy or upfront surgery |
| COSD: | Cancer Outcomes and Services Dataset |
| CRF: | Case report form |
| CRUK: | Cancer Research UK |
| ECOG: | Eastern Co-operative Oncology Group |
| eGFR: | estimated Glomerular filtration rate |
| EORTC: | European Organisation for Research and Treatment of Cancer |
| ePOCS: | electronic Patient-reported Outcomes from Cancer Survivors |
| EQ VAS: | EuroQoL visual analogue scale |
| EQ-5D-5L: | EuroQoL 5 dimension 5 level QoL questionnaire |
| FACT-G: | Functional Assessment of Cancer Therapy – General |
| FACT-O: | Functional Assessment of Cancer Therapy – Ovarian |
| FIGO: | International Federation of Gynaecologists and Obstetricians |
| FOP: | Fear of progression |
| HADS: | Hospital Anxiety and Depression Score |
| HR: | Hazard ratio |
| HRQoL: | Health related Quality of life |
| ICD: | International classification of diseases |
| IPG: | Interventional Procedure Guideline |
| MDRD: | Modification in diet in renal disease |

| | |
|---|---|
| MRC: | Medical Research Council |
| MRSA: | Methylene Resistant Staphylococcus Aureus |
| NACT: | Neoadjuvant chemotherapy followed by surgery |
| NCEPOD: | National Confidential Enquiry into Patient's Outcome and Death |
| NHS: | National Health Service |
| NICE: | National Institute for Health and Care Excellence |
| OS: | Overall survival |
| PCI: | Peritoneal carcinomatosis index |
| PDS: | Primary debulking surgery |
| PFS: | Progression free survival |
| PRO: | Patient reported outcomes |
| PROMs: | Patient reported outcome measures |
| PS: | Performance status |
| QLQ-C30: | Quality of life questionnaire – general cancer module |
| QLQ-OV28: | Quality of life questionnaire – ovarian cancer module |
| QoL: | Quality of life |
| R0: | No gross residual disease (complete debulking / cytoreduction) |
| R1: | < 1 cm residual disease (optimal debulking / cytoreduction) |
| R2: | ≥ 1 cm residual disease (suboptimal debulking / cytoreduction) |
| RCT: | Randomised controlled trials |
| RD: | Residual disease |
| REDcap: | Research electronic database capture |
| RIFLE: | Risk, Injury, Failure, Loss of function and End stage kidney disease |
| RR: | Relative risk |
| SCS: | Surgical complexity score |
| SOCQER: | Surgery in advanced ovarian cancer: quality of life evaluation research |
| UOB: | University of Birmingham |
| USA: | United States of America |
| VTE: | Venous thromboembolism |
| WHO: | World Health Organisation |

## Introduction to the thesis:

This thesis considers peri-operative morbidities, Quality of life (QoL) and survival outcomes following surgery for advanced ovarian cancer.

**Chapter 1** provides a background literature review covering the role of surgery in advanced ovarian cancer, associated morbidities, treatment approaches and survival outcomes.

**Chapter 2** is a systematic review of QoL following surgery in ovarian cancer and provides up to date information on current knowledge on QoL following ovarian cancer surgery.

**Chapter 3** discusses the prospective observational study: SOCQER-2 (Surgery in advanced Ovarian Cancer: Quality of life Evaluation Research) with its aims, methodology and results.

**Chapter 4** discusses details of an investigation of incidence of Acute Kidney Injury (AKI) in the same cohort of patients during their treatment for advanced ovarian cancer.

**Chapter 5** provides the salient findings from each chapter and summarises the thesis.

## Statement of contribution:

This thesis is based on a prospective observational study: SOCQER-2.

My contribution towards the thesis is as below:

**Chapter 1**: This is a review of available literature independently completed by myself (SK), based on literature searches through OVID (Medline and EmBASE) using key words to identify role of debulking surgery in management of ovarian cancer.

**Chapter 2**: Systematic review: I wrote the protocol, conducted the literature search and was joined by a 2nd reviewer, Joanna Long (JL) in identifying and selecting appropriate studies for the systematic review. I conducted all statistical analysis of the data in Review Manager for meta-analysis. I wrote the manuscript, edited and submitted it for peer reviewed publication, supervised by Sudha Sundar (SS), Sean Kehoe (STK) and Carole Cummins (CC). I prepared and submitted peer review comments and edited the manuscript accordingly. This chapter has been published as Kumar, S., J. Long, S. Kehoe, S. Sundar and C. Cummins (2019). "Quality of life outcomes following surgery for advanced ovarian cancer: a systematic review and meta-analysis." Int J Gynecol Cancer (Kumar et al., 2019).

**Chapter 3**: The protocol for this study (SOCQER-2) was already drafted before I joined the project. I made contributions towards improving the protocol, improved case report forms, visited sites for initiation, collected and reviewed the data received from each centres and cleaned the data based on best available information. The data collection and its relevance were supervised by SS and CC. I

added additional tools for appropriate analysis of the data (Level of disease & Clavien-Dindo classifications for grading morbidities). The outline of sample size calculation was provided by CC who calculated it to meet NICE (National Institute for Health and Care Excellence) requirements. I communicated with all teams contributing to the data and managed the online REDcap database for clinical data throughout the duration of data collection. I used SPSS to analyse the data and provided results except for Kaplan Meier plot and Cox regression models for Hazard ratio for survival (CC). CC also contributed the general linear repeated measures model, for complete cases, used to analyse QoL data.

**Chapter 4**: I conceived the project as an extension of SOCQER-2 (AKI in ovarian cancer surgery), designed the study and discussed this with my supervisors and with Lorraine Harper (Professor of Nephrology), to provide a structure to the data collection. I prepared the case report forms, developed REDcap database with IT support (GR) and communicated to all trainees at each centre to ensure the completion of database. I analysed the results using SPSS independently and produced results and wrote the chapter. CC advised me on multivariate analysis (forward stepwise regression models).

# CHAPTER 1:
# INTRODUCTION

Ovarian cancer is the most lethal among gynaecological cancers. According to the United States of America (USA) statistics 2011, ovarian cancer incidence was approximately 1/4$^{th}$ of all gynaecological malignancies, but nearly half of the deaths among gynaecological cancers were due to ovarian cancer (Siegel et al., 2011). In the United Kingdom (UK), on average, 7400 women are diagnosed with ovarian cancer every year and nearly 4100 women die each year (CRUK, 2019). Surgery, aiming to remove tumour mass and platinum-based chemotherapy is the mainstays of treatment. The surgical resection of the tumour helps to remove most of the chemo-resistant and necrotic mass, thereby, making the chemotherapy more efficient (Hoskins, 1994). The surgical approach towards cytoreduction has seen a significant change in the last 15 years. Many centres of European countries and the USA have published their results backing up the aggressive approach towards maximal cytoreduction (Aletti et al., 2006, Chi et al., 2006, Eisenhauer et al., 2006, Chi et al., 2009, du Bois et al., 2009a). Their results from retrospective observational studies demonstrate the inclusion of extensive upper abdominal surgery and resections of all possible gross disease improve progression free survival and overall survival. However, it is not clear if there is an element of selection bias in such studies. A Cochrane review investigating the utility of extensive surgery compared to standard surgery found only low quality studies reporting the survival advantage due to extensive surgery (Ang et al., 2011). This review has not been updated since first publication.

The finding of better cytoreduction rate and improved survival by trained gynaecological oncologists performing surgery at higher volume tertiary centres led to increased centralisation and utilization of higher complexity surgery for advanced ovarian cancer (du Bois et al., 2009b, Leandersson et al., 2017) and the current goal of cytoreduction, since the paradigm shift, is to achieve no visible residual disease towards improving outcome from ovarian cancer surgery.

In the UK, there is considerable variation in the practice of an aggressive surgical approach towards the treatment of advanced ovarian cancer (Barton et al., 2013, Naik et al., 2016). Some of the most important factors are varying opinions from surgeons based on their individual training, experience, and most importantly, lack of robust evidence that can be used to inform evidence based practice.

The uncertainty regarding the impact of extensive surgery on patients' QoL may be the other factor restricting the use of extensive surgical approach as the data on this subject from multicentre studies are sparse. The patient reported outcomes (PRO) of this intervention have not been reported previously in a systematic review. Due to the uncertainties in the quality of life (QoL) outcomes, evidence based local and national policies in support of such a surgical approach is lacking. Therefore, appropriately designed studies are needed to fulfil the gap in our knowledge with regard to the impact of extensive surgery for ovarian cancer on the quality of life of these patients. The patient reported outcome measures (PROMs) are validated tools specifically designed to understand the effect of such interventions and have been increasingly included in clinical trials as a primary or secondary endpoint. However, frequently, they are not reported well (Schandelmaier et al., 2015, Mercieca-Bebber et al., 2018). Additionally, The National Cancer Institute and the

Food and Drug Administration also advise the inclusion of PRO as an effective endpoint in clinical trials (Sloan et al., 2007, FDA, 2009, Basch et al., 2015). These domains not only have extraordinary value in evaluating the effectiveness and safety of treatment outcome, but they are also important for policymakers in implementation of quality improvement programmes.

Evolving international utilization and support for aggressive surgery in ovarian cancer has prompted National Institute for Health and Care Excellence (NICE) to develop a guideline for extensive (ultra-radical) cytoreduction surgery for advanced ovarian cancer in the UK (NICE IPG470). However, concerns regarding safety and efficacy of extensive surgery were raised. Selected centres were permitted to perform extensive surgeries with appropriate arrangements for clinical governance while calling for research to provide evidence as QoL outcomes. Since then, a few centres in the UK have reported the survival and morbidity outcomes of such extensive surgeries in advanced ovarian cancer (Fotopoulou et al., 2016, Turnbull et al., 2017, Phillips et al., 2019). A feasibility study by Soo Hoo et al, also highlighted that collecting PRO after surgical intervention in advanced ovarian cancer is acceptable and possible with results pointing towards no harmful effect on patient's quality of life after extensive surgery (Soo Hoo et al., 2015). Following this, NICE commissioned a prospective observational study to explore the province of PRO after extensive surgery comparing the result against the standard surgery for advanced ovarian cancer.

The international multicentre, prospective, population linked observational cohort study, "Surgery in advanced Ovarian Cancer: Quality of life Evaluation Research (SOCQER-2)", which also explores the patient's characteristics, extent of the disease load, types of treatment and post-operative morbidity, would allow an informative discussion of some of the unexplored queries related to the extensive surgery in ovarian cancer. Further, population linked analysis of the data (not discussed in this thesis) would provide a good insight into the variance in regional practice and resource utilization. The results from this research would also aim to provide some precious information for future surgical practice and guide patients and health care providers in clinical decision making and further research.

We addressed the questions regarding the impact of surgery on patients QoL by 1) conducting a systematic review investigating PRO after surgery 2) conducting a multicentre prospective study and 3) investigating post-operative morbidities and specifically the impact on renal function through a linked study SOCQER2-AKI.

## Epidemiology:

Worldwide, estimated prevalence of ovarian cancer cases in 2018 is 295,414 and estimated mortality from ovarian cancer is 184,799. The estimated annual prevalence in Europe and UK is 67,771 and 6407 respectively and estimated mortality remains about 44,576 and 4155 respectively (Ferlay et al., 2019). According to USA statistics 2011, ovarian cancer incidence was approximately 1/4$^{th}$ of all gynaecological malignancies, but nearly half of the deaths among gynaecological cancers were due to ovarian cancer (Siegel et al., 2011). In the UK, ovarian cancer is reported to be the 6$^{th}$ most common cancer among women with

almost 7500 new diagnosis (2016) and over 4100 deaths (2017) each year. The incidence of ovarian cancer increases according to the age and approximately 74% of the cases were diagnosed in women aged 55 and over with highest rate reported between 75 to 79 years of age. The age standardized rate is higher in white females (17.4 – 18.1) compared to Asian females (9.2 – 15.5) and Black females (6.6 – 12.1) per 100,000 (CRUK, 2019).

As with most cancers, survival for ovarian cancer is improving. The Office for National Statistics for England and Wales reported a net five-year survival of 46% and net 10 year survival of 34% for patients diagnosed between 2010 and 2011. The survival was reported to decrease sharply along with FIGO staging at diagnosis. Five-year survival was about 93% at stage 1, 68% at stage 2, 27% at stage 3 and only 13% at stage 4 (CRUK, 2019). In recent data from International Cancer Benchmarking Partnership (ICBP), the 5-year age-standardized net survival estimate for patients diagnosed between 2010 – 2014 is 44.9% (95% CI 44.1 – 45.7), which is equivalent to Ireland (44.8%) and slightly better than New Zealand (43.3%), but lower than Norway (54.5%), Australia (52.1%), Canada (49.3%) and Denmark (48.8%) (Arnold et al., 2019).

In the annual report by the Chief Medical Officer, 2014, the low survival rate in the UK was mainly attributed to lower stage-specific survival of patients with stage 3 and 4 ovarian cancer due to treatment variation being the main contributor. The report highlighted the consistent evidence base for achieving “no visible residual disease” after debulking surgery as most important predictor for survival since the mid-1970s and stated this as the goal for surgical treatment. However, major

challenges were outlined related to patients, surgeons, and the organizations providing service within NHS (Davies, 2015).

## Principle and current state of knowledge advocating surgery in advanced ovarian cancer:

Surgery for solid cancers is limited to loco-regional disease or surgery for palliation of symptoms. Exceptions to this include excision of liver metastasis for colorectal cancer (Rees et al., 2008). However, surgery in ovarian cancer is completely unique compared to other solid cancers in the use of cytoreduction. The spread of the disease typically occurs on the peritoneal surface and to a great extent, these remains superficially invasive before invading through the organ or involving other parts of the body. The complex structure of peritoneal folds, ligaments and dependent spaces within the peritoneal cavity allows the flow of metastatic malignant cells along with peritoneal fluid current (Meyers et al., 1987). The negative pressure generated within the peritoneal cavity due to breathing movement allows cells to move, deposit, and grow under diaphragmatic spaces commonly and is only identified by meticulous inspection and evaluation of peritoneal surfaces. Knowledge of this metastatic spread pattern and usually superficial invasive nature of ovarian cancer provides the foundation for cytoreductive surgery. Cytoreductive surgery should include removal of the uterus, both fallopian tubes, both ovaries and omentum since it is known that even normal-looking omentum can harbor microscopic disease (Young et al., 1983), along with resection of any peritoneal deposits or other organs involved with metastasis keeping surgical safety and limitations in principle. Surgery alone is not curative but it helps in the diagnosis and staging of the disease. It further aims to remove the tumour mass as much as

possible and therefore removes most of the chemo-resistant and necrotic mass, thereby, making the chemotherapy more efficient (Hoskins, 1994, Keating et al., 2013). In addition, it helps in the assessment of the status of the disease and also in palliation. The 3rd International Gynaecologic Cancer Intergroup Ovarian Cancer Consensus Conference defined the goal of cytoreduction surgery to achieve no visible residual disease (du Bois et al., 2005).

The surgical procedures utilized for cytoreduction have been described differently by various institutions and therefore different nomenclatures are in use to describe the extent of surgery. Commonly, the terms “radical surgery”, “extensive surgery”, “ultra-radical surgery” or “supra-radical surgery” are used by various authors interchangeably. The standard and extensive surgery are on a continuum and a Cochrane review described this as three types of surgery: standard surgery, radical surgery and supra-radical surgery (Ang et al., 2011).

Standard surgery is defined as hysterectomy, bilateral adnexectomy, excision of pelvic peritoneum, total omentectomy, appendicectomy, removal of bulky pelvic and para-aortic lymph nodes and simple peritonectomy. Radical surgery includes en-bloc removal of the uterus, adnexae, the pelvic peritoneum, recto-sigmoidectomy and simple peritonectomy. When the surgery includes extensive peritonectomy, partial resection of the diaphragm, other bowel resections, resections of sub-capsular liver metastasis, cholecystectomy, splenectomy, distal pancreatectomy or partial gastrectomy, it is described as supra-radical surgery (Pomel and Dauplat, 2004).

Aletti et al. 2007, from the Mayo Clinic, described the surgery with a complexity score with an attempt to define the complexity of surgery and its relation to post-

operative morbidity, mortality, length of stay and ability to receive chemotherapy. A range of procedures were given scores ranging from 1 – 3. A score of 1 – 3 is classified as low complexity, 4 – 7 as moderate and 8 or above as high complexity score (Aletti et al., 2007b).

The National Institute for Health and Care Excellence has defined the surgeries as below:

Standard surgery or radical surgery – It involves hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, retroperitoneal lymphadenectomy up to the renal veins and may include en-bloc resection of the recto-sigmoid colon with colostomy or primary anastomosis and simple peritonectomy.

Extensive or ultra-radical surgery – This is a continuum of standard (radical) surgery that may involve some of these extended procedures such as stripping of the diaphragm, extensive stripping of the peritoneum, multiple resections of the bowel (excluding localised colonic resection), liver resection, partial gastrectomy, cholecystectomy, splenectomy and resection of the tail of the pancreas (NICE IPG470).

## The evolution of the concept of surgical cytoreduction:

The use of surgery to reduce the cancer bulk has been known for nearly 100 years. Meigs et al. 1934 first reported the use of debulking concept (Meigs, 1934) and Munnell et al., 1968 reported outcome of his three case series where surgical procedures were carried out during 1922 to 1943 and again from 1944 to 1951. They first reported that increasing the surgical resection efforts with the intention to "remove as much as possible" in the case series of 235 patients treated between

1952 to 1961, improved the survival of their patients from 28% to 40%. One of their conclusions was the improvement in survival of those cases were not due to earlier diagnosis, favorable mix of cases or chemotherapy but due to more frequent radiotherapy (used at that time) and more aggressive and extensive surgery (Munnell, 1968). Munnell also advocated the practice of maximal surgical resection for the treatment of ovarian cancer in the future. Other studies also reported that overall survival in advanced ovarian cancer was inversely proportional to the residual tumor volume after primary therapy and resectability of the tumour was enhanced by chemotherapy (Villasanta and Bloedorn, 1968, Griffiths et al., 1972). Griffiths et al., in 1975 reported on the size of residual tumour and stated that tumour of less than 1.6 cm was inversely proportional to the survival time. Survival was uniformly poor if residual tumour size was more than 1.5 cm irrespective of the total tumor volume (Griffiths, 1975).

After this study, multiple studies validated this finding over next 2 decades, however, some of them looked at survival and effects of different chemotherapy regimen and used the criteria of residual disease less than or more than 2 cm (Delgado et al., 1984, Pohl et al., 1984, Piver et al., 1988, Gershenson et al., 1989). Gershenson et al., also discussed the superiority of primary cytoreduction surgery over interval cytoreduction surgery (Gershenson et al., 1989). Hacker et al. in 1983 used the classification of residual disease as suggested by earlier research and also added a subgroup where residual disease was less than 0.5 cm. The data were based on small number of participants but it showed 66% of optimal cytoreduction and a median survival of 40 months in the group of patients with cytoreduction of less than 0.5 cm, 18 months in cytoreduction group between 0.5 cm to 1.5 cm and 6 months

in group of patients with RD of more than 1.5 cm (Hacker et al., 1983). Krag et al. discussed the predictive factors for long-term survival and suggested that grade, stage and primary tumour size were the only independent prognostic factors. In a cohort of 85 patients with 45% optimal cytoreduction rate (less than 2 cm), overall 5-year survival was reported to be 26%, with a median survival of 33 months (Krag et al., 1989).

The re-analysis of the data of GOG protocol 52, which examined the outcome of 349 patients who had cytoreduction to less than 1 cm residual disease and randomised to Cyclophosphamide and Cisplatin with or without Doxorubicin arms (Omura et al., 1989) brought some new insight into the possible role of other prognostic factors which may exist. As only those patients who had residual volume of less than 1 cm after primary cytoreduction surgery were eligible for the study, it was possible to evaluate the effect of their characteristic at the time of presentation and findings at the surgery. The univariate and multivariate analysis of the data suggested that cytoreduction to less than 1 cm was not the only important prognostic factor but other factors also influence the recurrence and overall survival of these patients. One of the important features was the tumor volume and location of the disease at the time of presentation as the patients presenting with higher tumor volume had poorer survival in spite of reduction to the same small volume disease. Age at presentation, histological grade and number of residual lesions were also suggested to be important. The predictive value of disease load over the omentum regarding the extent and aggressiveness of the disease was also reported (Hoskins et al., 1992). The same author evaluated the outcome of 294 patients with stage III ovarian cancer under GOG protocol 97 and reported outcome on sub-

optimally debulked patients randomised for different doses of cisplatin and cyclophosphamide (McGuire et al., 1995). The initial tumor diameter and residual tumor diameter were reviewed and patients were grouped by residual tumor diameter. A multivariate analysis considering residual tumor diameter, age, histologic grade, performance status and ascites showed that among patients with residual disease diameter > 1 cm, smaller volume disease of less than 2 cm had a clear survival advantage over the patients with larger than 2 cm residual disease. All those with a residual diameter of more than 2cm had equivalent survival outcome (Hoskins et al., 1994).

In 1998, Eisenkop et al. published the result of his feasibility prospective study to determine the possibility of surgical elimination of all visible disease in patients with stage IIIC and IV epithelial ovarian cancer. 163 consecutive eligible patients with advanced stage disease were included in the study and underwent primary cytoreduction surgery. 85% of the patients had a complete cytoreduction and 13% had optimal (<1cm) cytoreduction. The study methodically described the technique of cytoreduction surgery. The vast majority of patients underwent complex procedures like en-bloc resection of pelvic organs and modified posterior exenteration, bowel resection, pelvic and para-aortic node removal, peritoneal stripping and excision or ablation of mesenteric or serosal disease in addition to the total resection of reproductive organs and omentum. More than 40% of the patients needed upper abdominal surgery including diaphragmatic stripping or resection, liver resection, splenectomy and excision of the tail of pancreas. The overall morbidity was observed in 68 (41.7%) patients and 3 (1.8%) patients died within 30 days after surgery. The median overall survival and 5-year survival rate for the

cohort was 54 months and 48% respectively (Eisenkop et al., 1998). The study not only demonstrated the overall improved survival but also supported the possibility of complete cytoreduction with maximal surgical efforts and described postoperative morbidity. It also supported the practice of ultra-radical procedure and provided the new goal of optimal cytoreduction definition. The author discussed that the biological nature of the tumor can possibly be overcome and sometimes negated with the use of extensive cytoreduction procedures. In another study by Kuhn et al., 1998, 107 patients treated between 1989 to 1995 were grouped into 2 groups: group-A (n=41) had upper abdominal procedures and group-B (n=66) did not have upper abdominal procedures. They demonstrated that morbidities are higher in group-A patients, specifically for those who required other upper abdominal procedures such as splenectomy, cholecystectomy and tail of pancreas resection. In terms of survival, there was no difference between the two groups, however within the groups, patients who had complete debulking with no residual disease had a clear survival advantage than those who had residual disease after the surgery (Kuhn et al., 1998).

In 2002, Bristow et al published a large meta-analysis containing 6885 patients from 81 cohorts having advanced-stage ovarian cancer and included the patients treated with primary cytoreduction surgery and chemotherapy between 1989 and 1998. The primary outcome was to evaluate the effect of maximal cytoreduction surgery and other prognostic factors on survival. After controlling for the other factors included in the study, it demonstrated a strong positive association of 5.5% increase in survival with every 10% increase in the proportion of patients who underwent maximal cytoreduction surgery. The data suggested a median survival of 33.9 months in

centres with >75% cytoreduction and 22.7months in centres with cytoreduction of 25% or less. As rates of successful maximal cytoreduction are usually possible only in expert centers treating advanced-stage ovarian cancer cases, it was also discussed as one of the important factor to be considered in future to improve overall survival. The platinum dose intensity and cumulative platinum dose did not affect the survival data significantly (Bristow et al., 2002).

Paclitaxel was introduced in 1989, but it was not until 1996 when the combination of platinum and taxane based combined chemotherapy was considered the primary choice of treatment (McGuire et al., 1989, Thigpen et al., 1994, McGuire et al., 1996). Studies comparing efficacy of cisplatin and paclitaxel with carboplatin and paclitaxel reported similar tumor response rate and survival, but the carboplatin containing regimen was tolerated better by patients as it caused less gastrointestinal and neurological toxicities and the global quality of life score was statistically significant (du Bois et al., 2003, Ozols et al., 2003). Since then, carboplatin and paclitaxel formed the first choice of chemotherapeutic intervention.

## Cytoreduction surgeries and survival in platinum - taxane era: A paradigm shift

Since the standardized chemotherapy in ovarian cancer consisting carboplatin and paclitaxel came in effect, various studies evaluated and reported survival advantage for post-operative no residual disease status for progression free survival (PFS) and overall survival (OS) as listed in Table 1. However, Eisenhauer 2006 and Chi D S 2009, retrospectively analyzed outcome data for cytoreduction rate and residual disease status following a change in their policy towards a surgical approach in debulking surgery i.e. the introduction of extensive surgical resection. A significant

change in optimal cytoreduction rate associated with improved median PFS and OS was demonstrated (Table 1) (Eisenhauer et al., 2006, Chi et al., 2009). Post-operative morbidities were also reported by some authors as discussed later in the thesis.

A Cochrane systematic review by Elattar et al., 2011 reported the prognostic importance of complete cytoreduction in primary surgery for advanced ovarian cancer in studies where multivariate analysis was undertaken to evaluate effect of residual disease size on survival and studies had at least 100 participants. Patients with no visible residual disease had prolonged PFS and OS. Patients with residual tumour size of less than 1 cm also had a survival advantage when compared to patients with residual disease of more than 1 cm. They concluded that no visible residual disease should be the goal of debulking surgery and where it is not possible, an optimal residual disease status (<1cm) should be the surgical goal (Elattar et al., 2011).

Table 1 below shows some of the studies reporting on PFS and OS in their cohorts between 2001 to 2015, demonstrating the effect of residual disease on survival.

Table 1: Summary of cytoreduction surgeries and survival in platinum - taxane era.

| Study | Cytoreduction rate (R0 – No gross residual, R1 – RD less than 1 cm, R2 – RD >1 cm) | Median PFS | Median OS | Prognostic markers / Notes / Reference |
|---|---|---|---|---|
| **Ozols 2003**<br>**All patients had residual disease less than 1 cm.**<br>**N=792**<br>**Group 1: Cisplatin + Paclitaxel**<br>**Group 2: Carboplatin + Paclitaxel**<br>**(Data analysis based on residual disease volume)** | R0 – 36%<br>R1 – 64% | 34 months (approx.)<br>17 months (approx.) | Not reached at 60 months<br>46 months | (Ozols et al., 2003) |
| **Chi DS 2006**<br>**All patients had primary debulking surgery**<br>**N=465** | R0 – 14%<br>R1 – 36%<br>R2 – 50% | NA | R0 – 106<br>R1 (<0.5 cm) – 66<br>R1 (0.6-1 cm) – 48<br>R2 (1-2 cm) – 33<br>R2 (>2 cm) – 34 | Residual disease<br>Age<br>Ascites<br><br>(Chi et al., 2006) |
| **Aletti 2006** | Optimal - 67.5% | NA | 5 year overall survival – 35% | Optimal Residual disease<br>(Aletti et al., 2006) |
| **Eisenhauer 2006**<br>**Patient grouped as optimal and suboptimal pre-year 2001 and after 2001 (change in use of extensive surgery, all group 1 patients were post 2001)**<br>**N=262**<br>**Group 1 - optimal post 2001 (n = 57),**<br>**Group 2 - optimal pre 2001 (n = 122),**<br>**Group 3 - pre/post 2001 (n = 83)** | (R0 +R1) - 68%<br>R2 – 32% | (R0+R1) – 23 months<br>R2 – 11 months | Median OS –<br>Group1 (Extensive surgery) – Not reached at 68 months<br>Group2 (Standard surgery) – 84 months<br>Gr3 – 38 months | Ascites<br>Stage IV<br>Residual disease<br><br>(Eisenhauer et al., 2006) |
| **Hockel M 2006** | R0 – 72/74 (97%) | 5-year PFS – 56%<br>(95% CI: 42-69) | 5-year OS – 56%<br>(95% CI: 42-70) | Morbidity 66%<br>(Hockel, 2006) |
| **Armstrong 2006** | 100% optimal<br>R0 - 37%<br>R1 – 63% | IV – 18.3m<br>IP – 23.8m | IV – 49.7m<br>IP – 65.6m | (Armstrong et al., 2006) |
| **Wimberger 2007** | Optimal - 32%<br>Suboptimal - 38%<br>Rest were IIB - IIIB | NA | Median OS<br>Optimal – 37m<br>Suboptimal – 31m | (Wimberger et al., 2007) |
| **Winter III 2007**<br>**Stage III**<br>**N= 1895**<br>**Retrospective data analysis from 6 prospective randomised GOG trials** | R0 – 437<br>R1 – 791<br>R2 – 667 | R0 – 33<br>R1 – 16.8<br>R2 – 14.1 | R0 – 71.9<br>R1 – 42.4<br>R2 - 35 | Age, PS, tumour histology, residual tumour<br><br>(Winter et al., 2007) |

| Study | Cytoreduction rate (R0 – No gross residual, R1 – RD less than 1 cm, R2 – RD >1 cm) | Median PFS | Median OS | Prognostic markers / Notes / Reference |
|---|---|---|---|---|
| **WinterIII 2008**<br>**Stage IV**<br>**N=360**<br>**Retrospective study, Primary debulking followed by 6 cycles of Platinum and Taxane** | R0 – 29<br>R1 – 78<br>R2 – 253 | R0 – 20.1<br>R1 – 13.1 | R0 – 63.1<br>R1 – 28.7 | histology, malignant pleural effusion, intra-parenchymal liver metastasis, and residual tumour size (Winter et al., 2008) |
| **Chi DS 2009**<br>**N=378**<br>**Group 1 1993-1996 – 100% standard (n=168)**<br>**Group 2 2001 -2004 – 38% Extensive (n=210)** | R0 –<br>Group 1 11%<br>Group 2 – 27%<br><br>Optimal cytoreduction (<1cm)<br>Group 1 – 46%<br>Group 2 – 80% | 5-year PFS rate:<br>Group 1 – 14%<br>Group 2 – 31%<br><br>(HR 0.76; 95% CI 0.60 to 0.95, p=0.01) | 5-year OS rate<br>Group 1 – 35%<br>Group 2 – 47%<br>(HR 0.76; 95% CI 0.59 to 0.99, p=0.03)<br>Median OS<br>Gr1 – 43 months<br>Gr2 – 54 months | (Chi et al., 2009) |
| **Du Bois 2009**<br>**Data from 3 prospective trials** | Optimal - 58% | Stage IIIC<br>R0 – 35m<br>R1 – 15.5m<br>R2 – 13.7m<br><br>Stage IV<br>R0 – 19 m<br>R1 – 13.5m<br>R2 – 11.5m | Stage IIIC<br>R0 – 81.1m<br>R1 – 35.6m<br>R2 – 30.7m<br><br>Stage IV<br>R0 – 54.6m<br>R1 – 26.2m<br>R2 – 23.9m | Residual disease<br>age,<br>performance status,<br>grade,<br>FIGO stage, histology<br><br>(du Bois et al., 2009a) |
| **Kommoss S 2010** | 47.2%<br>(Standard – 36%<br>Extensive – 64%) | Extensive vs Standard with R0 (HR=1.73, 95% CI: 1.06 to 2.84, p=0.028) | R1/R2 vs R0 –<br>HR 3.61 (1.97 – 6.61, p<0.01)<br><br>R0<br>Extensive vs standard surgery<br>HR 1.37, 95%CI 0.70 – 2.69 | (Kommoss et al., 2010) |
| **Chi DS 2010** | R0 – 30%<br>R1 – 60% | NA | Median OS - 57 months | (Chi et al., 2010) |
| **Peiretti 2010** | R0 – 44%<br>R1 – 56% | 19.9 months | 57.6 months | Age, FIGO stage, Residual disease<br>(Peiretti et al., 2010) |
| **Fu et al., 2014** | PDS | 3-year - 19.9%<br>5-year - 17.7% | 3-year OS - 42%<br>5-year OS - 33% | (Fu et al., 2014) |

## Concept of neoadjuvant chemotherapy (NACT) and interval/delayed debulking surgery:

The concept of interval debulking was discussed as early as in 1989 by Gershenson et al, where they suggested that primary cytoreduction is superior to interval cytoreduction surgery (Gershenson et al., 1989). There are some data available for induction chemotherapy which showed that there was approximately 6 months of survival advantage and 33% reduced risk of death even in cases where primary cytoreduction remained unsuccessful and patient received chemotherapy to decrease the tumour load and then had optimal cytoreduction without any significant morbidity or mortality (van der Burg et al., 1995). This highlighted the importance of the role of chemotherapy as a tool where primary cytoreduction surgery is not deemed suitable.

EORTC 55971 published its result in 2010 comparing NACT vs PDS. The total number of the patient studied were 670, recruited as a multi-center, non-inferiority randomised controlled trial with equivalent number of patients in both arms of study. The patients included had stage IIIC or IV ovarian cancer, primary peritoneal cancer or fallopian tube cancer diagnosed either by imaging or laparoscopy. The baseline characteristics in both arms were similar. There was evidence of tumour shrinkage in NACT group as only 37% of the patients had a tumour of more than 5 cm size compared to 74% in the primary debulking surgery group and this in turn resulted in 81% of optimal cytoreduction in NACT group versus 42% in the primary debulking surgical group. Interestingly, this difference in the rate of cytoreduction did not affect the median PFS or OS rate, although complete cytoreduction was an independent

prognostic factor. The median PFS was 12 months in both groups and the median OS was 30 months in the NACT group and 29 months in PDS group. However, perioperative and postoperative morbidity and mortality were significantly lower in the NACT group (Vergote et al., 2010). Following this EORTC study, Chi et al, from Memorial Sloan-Kettering cancer center published the data on their patients using the identical inclusion criteria as EORTC study and during the identical time interval. NACT was used as a primary treatment only if there were extra-abdominal disease or medical co-morbidities and/or advanced age of more than 85 years. 90% (n=285) of the patients had primary debulking surgery with stage IIIC or IV ovarian cancer and the optimal cytoreduction rate (<1cm) was achieved in 71% of the cases. They reported median PFS of 17 months and median OS of 50 months and concluded that primary debulking surgery should remain the first choice of treatment and NACT should be reserved only for those patients who are not suitable for surgery of where primary debulking is not deemed feasible (Chi et al., 2012).

A phase III non-inferiority randomised controlled trial (CHORUS MRC trial - Chemotherapy OR Upfront Surgery) was published in 2015. The 550 patients with stage IIIC and IV epithelial ovarian cancer were enrolled from 87 hospitals in the UK and New Zealand during 2004 and 2010. The primary outcome was overall survival and data were analysed in the intention-to-treat population. The PFS in primary surgery group and Primary chemotherapy group was 10.7 months and 12 months respectively (HR 0.91; 95%CI 0.76-1.09). The median OS was 22.6 months in primary surgical group and 24.1 months in NACT group. The patients in NACT group were 13% less likely to die at the given time interval (HR 0.87%; 95% CI 0.72

– 1.05). However, the perioperative and postoperative morbidities (24% vs 14%) and mortality (6% vs 1%) favoured the NACT group. It was recommended that NACT is non-inferior to primary surgery and given the benefit of reduced risk related to neoadjuvant chemotherapy, this should be considered as an acceptable standard of care for women with advanced ovarian cancer (Kehoe et al., 2015).

Given the evidence from the last 30 years of use of neoadjuvant chemotherapy, only 2 recent trials, EORTC 55971 and CHORUS MRC trial provide knowledge applicable to our current practice. It is worth noticing again that in these studies, in spite of achieving a nearly double the rate of optimum cytoreduction, the NACT group does not offer extra survival. A recent meta-analysis of the pooled individual patient data evaluated the long-term outcome and reported that NACT is not inferior to the primary debulking surgery and particularly beneficial in patients with higher disease burden and FIGO stage 4 disease (Vergote et al., 2018).

## Morbidity and mortality:

The concerns of morbidity and mortality after extensive surgery remains one of the factors that dissuade some surgeons from undertaking an extensive surgical approach towards treatment of advanced ovarian cancer in spite of having good quality data regarding the outcome from complete cytoreduction. There are many retrospective studies that addressed this question, but the present information is still suboptimal. The lack of uniform assessment criteria and reporting of the published studies makes its interpretation and applicability a difficult task. The case selection, basic characteristics of the patients, surgeon's skill, biological nature of the cancer and postoperative care are some of the other important aspects that are vital to

comprehend the morbidities associated with the surgery. Criteria for defining post-operative morbidity such as Clavien-Dindo classification are not consistently used across studies. Table 2 describes the frequencies of complications reported in some of the studies.

Table 2: Summary of reported morbidity/mortality after extensive surgery

| Complications (%) | Kuhn, 1998 (Kuhn et al., 1998) | Chi, 2010 (Chi et al., 2010) | Kommoss, 2010 (Kommoss et al., 2010) | Pieretti, 2010 (Peiretti et al., 2010) | Rafil, 2012 (Rafii et al., 2012) | Fotopoulou, 2016 (Fotopoulou et al., 2016) | Fagotti, 2016 (Fagotti et al., 2016) | Turnbull, 2017 (Turnbull et al., 2017) |
|---|---|---|---|---|---|---|---|---|
| **Pyrexia** | 51.2 | | 5.3 | | | | | |
| **Sepsis** | 12.1 | | | | | 3.4 | 7.2 | |
| **Return to theatre** | 12.1 | 3.5 | 13.2 | | | 3.4 | 3.6 | 3.7 |
| **VTE** | 9.7 | | 5.3 | 2.3 | | 5 | 5.4 | |
| **Minor complications** | | | | 28 | | | | |
| **Major complications** | 31.7 | 22 | 2.6 | 13 | | 18.6 | 58 | 6.7 |
| **Overall complications** | | | 26.4 | | 20.0 | | | |
| **Pleural effusion** | 63.4 | 39 | | 24 | | | 31 | |
| **Mortality (30/60 day)** | 12.1 | 1.4 | 0.0 | | 0.5 | 1.7 | 3.6 | 0.7 |

## Criticisms of surgery in advanced ovarian cancer:

This review of the literature strongly suggests that whether the treatment is primary debulking surgery or neoadjuvant chemotherapy followed by interval debulking surgery, almost all of the cases of advanced stage disease recur. Some cancers recur within a few months after the completion of chemotherapy and some patients are disease-free for a couple of years, as median PFS figures are around 12 to 17 months. In a proportion of cases, cytoreductive surgery is either not feasible or there is a failure to achieve optimal cytoreduction and not all the cases of ovarian cancer are sensitive to chemotherapy. These features allow substantial grounds to explore the possible reasons for the failure of different modalities of treatment and may guide towards the areas of future research.

**Relevance of tumour biology:** The biological nature of the disease is one of the most commonly discussed factors that may influence the outcome of the surgery and overall survival. It is believed that it is the nature of the disease which allows surgical resections to be successful rather than the skills of the surgeon (Hogberg, 1995, Crawford et al., 2005). In fact, Griffiths et al, while suggesting the inverse relationship in the size of residual disease and survival, also pointed out that the observed survival may be a manifestation of limited or less invasive tumour growth, which in turn makes tumour resectable (Griffiths, 1975). The most aggressive disease usually presents late and poses challenges during surgery and tends to recur sooner. Many authors have questioned this as prognostic markers of the disease vary among the studies and they frequently include age, histological type and grade, the initial burden of the disease and, of course, the extent of residual

disease after the surgery (Hoskins et al., 1992). According to the Goldie-Coldman hypothesis, there is a possibility of having at least one resistant phenotype during the tumour development and it may well be related to the tumour size. It explains that there are greater chances of harbouring mutant clones of cancer in larger tumour and these tumour mostly would have developed clones of resistant cells by the time of the diagnosis due to its genetic instability. The role of debulking is transparent, however, in spite of having an optimal debulking surgery and appropriate first line chemotherapy; patients are likely to relapse soon (Goldie and Coldman, 1979, Covens, 2000).

Horowitz et al, 2015, analysed 2,655 patient's data from GOG182 with the aim to evaluate if an aggressive surgical approach led to survival advantage. Patients with no macroscopic residual disease definitely had better PFS and OS, but after controlling for preoperative disease load, residual disease, patient's age, performance status and an interaction term for disease load and complexity score, complexity score itself was not an independent predictor of either PFS or OS (Horowitz et al., 2015). A prediction model for achieving no gross residual disease at surgery consisting of disease Score ($p<0.001$), stage ($p=0.009$), CA125 ($p<0.001$), ascites ($p<0.001$), and stage-age interaction ($p=0.01$) and suggested future performance of the prediction model using additional factors such as imaging and molecular profiling could be explored to provide useful information (Horowitz et al., 2018).

**Measurement of residual disease:** The definition of optimal debulking has remained a controversial subject. Currently, less than 1 cm of the residual disease is considered optimal. With advances in the practice of extensive surgical method, the

boundary has shifted towards “no residual disease” as the goal of cytoreduction surgery. My review of the literature has not provided information on standardisation of the estimation of residual disease. One simulated patient model study evaluated the accuracy and inter-observer variability of intraoperative tumour measurements in ovarian cancer and reported that surgeons underestimated the tumour diameters and there is potential that the residual disease could be underestimated in 20% to 25% of the patients (Prefontaine et al., 1994). A prospective observational study into the visual estimation of residual disease after PDS or NACT suggested that approximately 14% of normal-looking peritoneum during surgery after neoadjuvant chemotherapy had microscopic disease on histological examination (Hynninen et al., 2013). Hence, it is possible that studies surrounding cytoreduction surgery have under-reported the residual disease load. As currently with the drive for complete cytoreduction, “the more we look for, the more disease we find”. However, it remains objective that complete or near-complete cytoreduction is associated with the best possible survival advantages.

**Retrospective data:** There is considerable difficulty in designing randomised trials with surgical arms due to “ethical issues include lack of equipoise among surgeons” – potential investigators unlikely to allow randomisation to different kinds of surgery. Therefore, only well designed prospective studies are currently possible. However, there are minimal numbers of such prospective studies. Most of the published studies providing the current evidence base are either case series from single or multiple centres or retrospective studies and therefore associated bias is inherent. While some prospective European studies are reporting lower PFS or OS and do not show a considerable difference in the outcome of either primary debulking or

interval debulking group (Vergote et al., 2010, Kehoe et al., 2015), retrospective North American studies still consider primary debulking surgery as the treatment of choice (Chi et al., 2012). The only reported difference is the higher complete cytoreduction rate in later studies. The variations in the practice among the surgeons pose another challenge in the reliability and acceptance of the published data.

## Quality of life:

The survival rate has remained the focus of nearly all the studies done to evaluate the effectiveness of the intervention. Health care providers and patients rightly have concerns regarding the quality of life of the patients undergoing interventions related to standard surgery, extensive surgery or chemotherapy. The pilot project, SOCQER-1 compared Patient reported outcome measures (PROMs) in 64 women with ovarian cancer, of which 24 had extensive surgery and found no statistically significant differences in PROMs in women undergoing standard or extensive surgery for ovarian cancer by the 9 months postoperative period. The potential effect of extensive surgery on QoL remains unknown. A better understanding of QoL and morbidity associated with surgical treatment will help the clinicians and patients make an informed decision on patient care.

In principle, the surgery helps to remove the bulk of tumour mass and therefore removes most of the tumours which chemotherapeutic drugs fail to reach. In addition, it clears out most of the chemo-resistant mass and host immune-competence is improved. It leaves the smaller size of active tissue where chemotherapy can be most effective and therefore side effects due to dose and

number of cycles can be minimised (Hacker, 1989, Keating et al., 2013). Evidence also supports use of neoadjuvant chemotherapy followed by debulking surgery and indicates this intervention is non-inferior but has advantage of reduced intra-operative and post-operative morbidities. The QoL outcomes of these interventions are unknown and therefore, data coming from SOCQER-2 study will be important in helping improve the care of patients worldwide and will inform future research.

In this thesis, first of all, I aim to conduct a systematic review of QoL following surgery in advanced ovarian cancer and evaluate all possible studies reporting on QoL both as primary or secondary outcomes with their methodology review and report what is known so far. Further to this, I will report on methods used in SOCQER-2 and its results in detail drawing conclusions on the impact of extensive surgeries on patients' QoL using EORTC QLQ-C30 and OV28. In an additional study of patient's morbidities, I then aim to study and report on incidences of acute kidney injury (AKI) during treatment of advanced ovarian cancer in the same group of patients. This has not yet been evaluated and knowledge on this subject is lacking in current literature.

# CHAPTER 2:
# QUALITY OF LIFE OUTCOMES FOLLOWING SURGERY FOR ADVANCED OVARIAN CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS.

[Published as "Quality of life outcomes following surgery for advanced ovarian cancer: a systematic review and meta-analysis." International Journal of Gynecologic Cancer (Kumar et al., 2019)]

## Abstract:

**Background:** Quality of life after ovarian cancer treatment is an important goal for patients. Complex debulking surgeries and platinum based chemotherapy are often required but the quality of life after surgery is rarely reported.

**Objectives:** To describe quality of life outcomes after surgery for advanced ovarian cancer in a systematic review and meta-analysis.

**Search strategy:** MEDLINE, EMBASE and CENTRAL through March 2019 with no language restrictions

**Selection criteria:** Included studies reported quality of life in women diagnosed with primary advanced ovarian cancer, fallopian tube cancer or primary peritoneal cancer undergoing cytoreduction surgery.

**Data collection and analysis:** Data on extent and timing of surgery, quality of life outcomes and surgical complications were extracted and study quality assessed.

**Main Results:** Three randomised controlled trials comparing primary surgery to neoadjuvant chemotherapy had heterogeneous quality of life outcomes with no difference between arms although there was a clinical improvement in global quality of life scores in both arms at 6 months compared to baseline. Data from two

observational studies showed no meaningful difference in the quality of life scores between patients undergoing standard or extensive surgery after 6 months.

**Conclusions:** There was no clinically important difference in the quality of life of patients undergoing either primary debulking surgery or neoadjuvant chemotherapy. There is insufficient evidence on quality of life outcomes of patients undergoing extensive or ultra-radical surgery compared with those undergoing less extensive surgery. Quality of life outcomes matter to patients but there is little evidence to inform patient choice regarding the extent of surgery.

**Keywords** Ovarian cancer, quality of life, extensive surgery, ultra-radical surgery, debulking surgery

## Introduction:

Whilst overall survival and progression free survival are critical outcomes for cancer patients, quality of life is of fundamental importance to patients (Bottomley, 2002). Health related quality of life refers to the effect of an illness and its therapy upon a patient's physical and occupational function, psychological state and social wellbeing which itself can influence treatment decisions (Osoba, 1994, Friedlander et al., 2016, Di Maio and Perrone, 2016). Standard treatment in advanced ovarian cancer comprises a combination of cytoreduction surgery and chemotherapy using carboplatin and paclitaxel (Jayson et al., 2014). Although considerable variations exist in international surgical opinion and practice (Eisenkop and Spirtos, 2001, Brand, 2011, Cibula et al., 2011, Barton et al., 2013, Naik et al., 2016), complex surgery is increasingly performed with the goal of complete cytoreduction which may include resections of the bowel and of disease on the liver, diaphragm and spleen.

Multiple studies have shown improved progression free survival and overall survival with complete cytoreduction (Eisenkop et al., 1998, Eisenhauer et al., 2006, Aletti et al., 2006, Chi et al., 2009, Elattar et al., 2011) however, initial disease burden remains a prognostic indicator (Horowitz et al., 2015). In a Cochrane review, low quality evidence shows a survival benefit with more extensive surgery, and differences in morbidity and quality of life outcomes of extensive surgery compared to standard surgery are still unclear (Ang et al., 2011).

Greater morbidity is associated with extensive surgery (Kuhn et al., 1998, Chi et al., 2010) but knowledge of the quality of life is lacking. Whether a patient has primary debulking surgery or neoadjuvant chemotherapy may also impact on quality of life. Understanding quality of life outcomes is critical given randomised controlled trial data on surgical extent is lacking. Robust estimation of survival benefit for any

individual patient undergoing extensive surgery is therefore challenging. The putative survival gain from extensive surgery might be offset by deterioration in quality of life as a result of increased morbidity. While much is known about the quality of life outcomes during or after chemotherapy (Vasey et al., 2004, Greimel et al., 2006, du Bois et al., 2010, Monk et al., 2014, Brotto et al., 2016), the impact on quality of life from surgery, particularly extensive surgery remains unknown.

The purpose of this systematic review and meta-analysis is to report patient reported quality of life after surgery in advanced ovarian cancer.

## Methods:

We searched Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to Present and EMBASE 1974 to 11th of March, 2019 and current edition of CENTRAL for eligible studies (SK, JL) with no language restrictions (Appendix-S1, page 44 ). Science Citation Index (Web of Science), www.clinicaltrials.gov and metaregister of controlled trials were searched. Reference lists of included studies were screened. Abstracts of meetings from International Gynaecological Cancer Society, British Gynaecological Cancer Society, European Society of Gynaecological Oncology, American Society of Clinical Oncology and Society of Gynaecological Oncology were searched. We included randomised controlled trials, non-randomised trials and prospective observational studies describing any quality of life measures as primary or secondary outcomes. Studies with women aged 18 and over, diagnosed with International Federation of Gynaecology and Obstetrics (FIGO) stages 3 or 4 epithelial ovarian cancer, fallopian tube cancer or primary peritoneal carcinomatosis undergoing cytoreduction surgery were included (Prat, 2014). Studies evaluating the

quality of life only in chemotherapy interventions, intraperitoneal chemotherapy or in recurrent ovarian cancer were excluded.

All identified references were transferred to EndNote bibliographic software and duplicated studies were removed. Two authors (SK, JL) independently reviewed all titles and abstracts and retrieved full text of selected studies. Two authors (CC, SS) reviewed articles where there was any uncertainty. The risk of bias was assessed using the Newcastle–Ottawa quality assessment scale for observational studies (GA Wells, 2008) and the Cochrane tool (JPT, 2011) for randomised controlled trials.

Data extracted included: author's details and citation index, publication year, country, study design, participants number, mean age, performance status, FIGO stage, histology, quality of life tools, quality of life scores at different time points, overall survival and progression free survival. Where appropriate, meta-analysis was carried out using random effects and study heterogeneity was assessed. Quality of life was described in the following sub-groups: primary debulking surgery vs neoadjuvant chemotherapy and standard vs extensive surgery. Quality of life scores were recorded as mean with standard deviation and a 10 point difference in the quality of life score was considered meaningful as per European Organisation for Research and Treatment of Cancer (EORTC) guidelines. Standard deviation values were calculated using the Cochrane tool if only standard errors were provided (JPT, 2011). The systematic review protocol was registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016048139).
A PRISMA statement and checklist for systematic reviews is provided in Appendix-S7, page 50 (Liberati et al., 2009).

## Results:

We identified a total of 10,220 records from the database search and other sources such as science citation index and abstract of meetings. After removing duplicates, we screened title and abstracts of 6464 records and excluded 6452, based on study characteristics, design and reported outcomes. Seven records were excluded after full text review. Five studies were included in the systematic review (Angioli et al., 2013, Kehoe et al., 2015, Soo Hoo et al., 2015, Fagotti et al., 2016, Greimel et al., 2013). The authors of all included studies were contacted for additional information (Kehoe et al., 2015, Greimel et al., 2013). The electronic search criteria, selection process flow diagram and list of excluded studies are given in appendices (S1, S2 and S3, page 44, 45 and 46).

Three included studies were randomised controlled trials comparing primary debulking surgery with neoadjuvant chemotherapy, evaluating quality of life as secondary outcomes (Kehoe et al., 2015, Fagotti et al., 2016, Greimel et al., 2013). Two prospective observational studies compared standard surgery and extensive surgery with quality of life as a primary endpoint (Table 3) (Angioli et al., 2013, Soo Hoo et al., 2015). All studies used the validated EORTC QLQ-C30 tool, and three of these additionally used QLQ-OV28 (Angioli et al., 2013, Soo Hoo et al., 2015, Fagotti et al., 2016). The randomised controlled trials had a low risk of selection and detection bias, but high or unclear risks regarding attrition and reporting of quality of life (Appendix-S4, page 47). There was an unclear or high risk of bias in the observational studies (Appendix-S5, page 48).

Table 3: Characteristics of included studies

| PDS compared with NACT | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Study** | **Country** | **Setting/Design** | **Study groups** | **Study population mean age** | **Number of participants** | **WHO Performance status at baseline** | **FIGO Stage** | **Outcomes** |
| Greimel 2013 | Europe/ Canada | Randomised controlled trial | PDS<br>vs<br>NACT | PDS = 62<br>NACT = 63 | N=404 (for QoL)<br>PDS = 203<br>NACT = 201 | 0 – 2 | III – IV<br>III – 74%<br>IV – 26% | OS, PFS, QoL |
| Kehoe 2016 | UK / New Zealand | Randomised control trial | PDS<br>vs<br>NACT | PDS = 66<br>NACT = 65 | N=457 (for QoL)<br>PDS = 230<br>NACT = 227 | 0 – 3 | III – IV<br>III = 75%<br>IV = 25% | OS, PFS, QoL |
| Fagotti 2016 | Italy | Randomised control trial | PDS<br>vs<br>NACT | PDS = 54<br>NACT = 55 | PDS = 55<br>NACT = 55 | 0 – 2 | IIIC – IV<br>IIIC – 89%<br>IV – 11% | PFS, OS, QoL, Postoperative complications |
| **Standard surgery compared to extensive surgery** | | | | | | | | |
| **Study** | **Country** | **Setting/Design** | **Study groups** | **Study population mean age** | **Number of participants** | **WHO Performance status** | **FIGO Stage** | **Outcomes** |
| Angioli 2013 | Italy | Prospective observational study | Standard surgery (Group 1)<br>vs<br>Ultra-radical surgery (Group 2) | Group 1 = 53.6<br>Group 2 = 63.9 | 80 ( 40 in each group) | 0 – 1 | III – IV<br>III – 82.5%<br>IV – 17.5% | QoL |
| Soo Hoo 2015 | UK | Prospective observational study | Standard surgery (Group 1)<br>vs<br>Ultra-radical surgery (Group 2) | Group 1 = 61<br>Group 2 = 63 | N=56<br>Group 1 = 32<br>Group 2 = 24 | ASA I – III | I – IV<br>Group 1:<br>I = 6 (18.8%)<br>II = 3 (9%).<br>IIIB = 1 (3 %)<br>IIIC – IV = 22 (68.8%)<br>Group 2:<br>IIIC – IV = 24 (100%) | QoL |

[WHO= World Health Organisation, FIGO=International Federation of Obstetricians and Gynaecologists, PDS= Primary debulking surgery, NACT= Neoadjuvant chemotherapy followed by surgery, OS=Overall survival, PFS= Progression free survival, QoL=Quality of life, ASA=American Society of Anaesthesiologists]

## Primary debulking surgery vs neoadjuvant chemotherapy (timing of surgery):

Greimel 2013 (EORTC55971 study) (Greimel et al., 2013), Kehoe 2015 (CHORUS MRC trial) (Kehoe et al., 2015) and Fagotti 2016 (SCORPION trial) (Fagotti et al., 2016) examined the quality of life outcomes in patients undergoing primary debulking surgery followed by adjuvant chemotherapy and neoadjuvant chemotherapy followed by surgery. EORTC55971 and CHORUS design and participant characteristics were similar regarding the process of selection, randomisation, follow-up and methods used in reporting the quality of life outcomes. EORTC55971 (Greimel et al., 2013), however, only reported outcomes from 27 out of 59 centres. Centres were included only if they were able to contribute 50% patient data at baseline and at least 35% at follow up. As a result, 337 out of 632 patients (53%), provided baseline data with subsequent loss of follow-up (Table 4) and the reported data is based on 212 patients (34%) at 6 months and 142 patients (22%) at 12 months. Quality of life data in the CHORUS MRC trial (Kehoe et al., 2015) is based on 52% and 53% of expected patients at 6 months and 12 months respectively. Patients in these trials had mean baseline EORTC QLQ-C30 global health scores of around 50. The SCORPION trial (Fagotti et al., 2016) selectively enrolled patients with high tumour load and had lower mean EORTC QLQ-C30 global health scores of around 33. All expected patients returned their quality of life data at baseline (n=110), as did 99 patients (90%) at $6^{th}$ cycle of chemotherapy and 95 patients (86%) at 6-month follow-up.

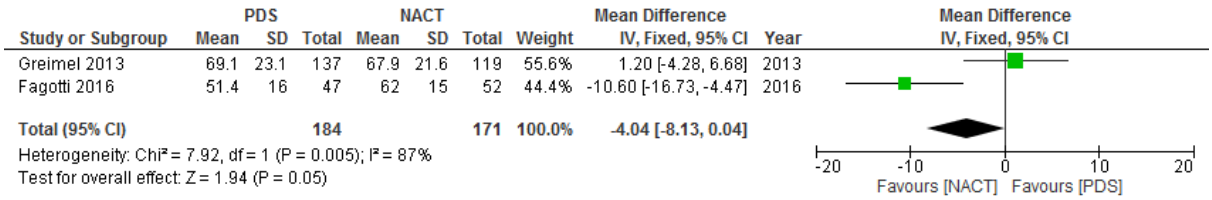
Across all included studies, 1064 patients were recruited, baseline quality of life data were available for 904 patients, with the attrition of up to 60% by 6 months (524 of eligible 871) and 49% (275 of eligible 563) by 12 months (Table 4). Despite

similar design, methods and attrition, the meta-analysis showed considerable statistical heterogeneity in global quality of life score in patients at all follow-up points. There were no statistically significant differences in baseline quality of life between arms although SCORPION patients had mean scores of around 33 compared to around 50 in the other trials. At the 6th cycle of chemotherapy, the SCORPION trial reported a significantly better quality of life in patients having neoadjuvant chemotherapy but there was no difference between arms in the EORTC55971 study (Figure 1a). At 6 months follow-up, patients in SCORPION and EORTC55971 reported no difference in global quality of life scores but CHORUS favoured NACT (Figure 1b). The meta-analysis of data from all three trials at 6 months follow-up showed no statistical difference (p=0.59) in the presence of important heterogeneity and similar results were noticed at 12 month follow-up in CHORUS and EORTC55971 (p=0.78, Figure 1c). Improvement in the quality of life score at 6 months compared to baseline was maintained at 12 months regardless of treatment received. As these studies were not designed to record the extent of surgery, it was not possible to analyse the quality of life data by extent of surgery.

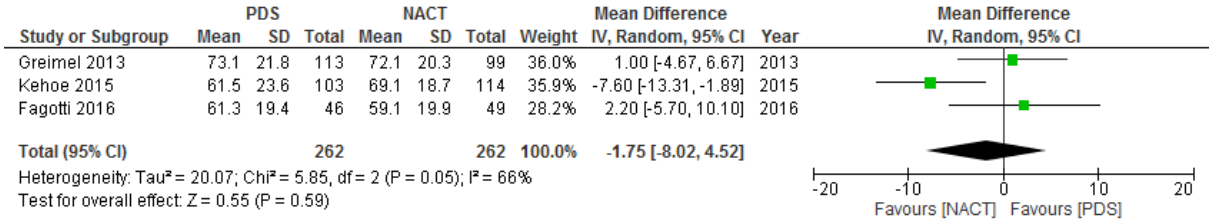
Table 4: Loss to follow-up rate in the studies comparing PDS and NACT

| | Greimel 2013 | % of participants expected to return QoL questionnaire | Kehoe 2015 | % of participants expected to return QoL questionnaire | Fagotti 2016 | % of participants expected to return QoL questionnaire | Overall | % of participants expected to return QoL questionnaire |
|---|---|---|---|---|---|---|---|---|
| **Number recruited in original study** | 632 | - | 550 | - | 110 | - | 1292 | - |
| **Number of patients participating in QoL study** | 404 | 64% | 550 | 100% | 110 | 100% | 1064 | 82% |
| **Baseline: questions returned / Expected to return** | 337/404 | 83% | 457/550 | 83% | 110/110 | 100% | 904/1064 | 85% |
| **6 months: questions returned / Expected to return** | 212/357 | 59% | 217/419 | 52% | 95/95 | 100% | 524/871 | 60% |
| **12 months: questions returned / Expected to return** | 142/311 | 46% | 133/252 | 53% | NA | NA | 275/563 | 49% |

## 1a. Global QoL score at 6th cycle (PDS vs NACT)




## 1b. Global QoL score at 6 months follow-up (PDS vs NACT)




## 1c. Global QoL score at 12 months follow-up (PDS vs NACT)

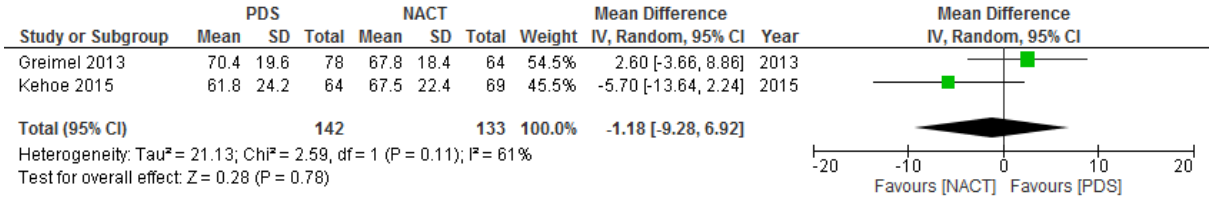



**Figure 1: Meta-analysis - Global QoL at 6th cycle of chemotherapy, 6 month & 12 month follow-up**

QoL = Quality of life; PDS = Primary debulking surgery; NACT = Neoadjuvant chemotherapy; SD= Standard deviation; CI = Confidence interval [Time points calculated approximately from methods to nearest to 6 months and 12 months]

**Standard vs Extensive surgery:** Two observational studies with an unclear or high risk of bias, Angioli 2013 (Angioli et al., 2013) (n=80), and Soo Hoo 2015 (Soo Hoo et al., 2015) (n=56), reported quality of life outcomes after standard (pelvic) surgery or extensive surgery. In both, patients undergoing pelvic surgery alone had lesser disease load than those undergoing extensive surgery. In Soo Hoo 2015 study, 9/32 standard surgery patients were FIGO stages 1 or 2 and 4/32 were not epithelial types, resulting in heterogeneity between standard and extensive groups. Angioli 2013 reported quality of life outcomes at 6 months, without any baseline data and patients in standard surgery group were younger. Soo Hoo 2015 included quality of life at baseline, 6 weeks, 3 months, 6 months and 9 months after surgery.

In Angioli 2013, there were no clinically meaningful differences in global quality of life at 6 months between groups; 75.8 in the extensive and 69.6 in the standard surgery group (p=0.002). In Soo Hoo 2015, baseline mean EORTC QLQ-C30 global health score was at 58 points for standard and at 63 points for extensive surgery. In the extensive surgery group, there was a clinically meaningful but not statistically significant 10 points fall (63 to 53) in global quality of life score at 3 months followed by gradual improvement at 6 months, returning to baseline values by 9 months. At 6 weeks, there was no difference in global quality of life or symptom burden compared to baseline, but a significant impairment was reported in functional quality of life for patients undergoing extensive surgery. In the standard surgery group, these variations were minimal.

## Patient reported symptoms

Three studies explored symptoms impacting on the quality of life (Greimel et al., 2013, Soo Hoo et al., 2015, Fagotti et al., 2016). Baseline symptom scores were highest for fatigue, insomnia and loss of appetite (n=503). Patients in EORTC55971 reported a clinically meaningful (statistical significance not reported) improvement in overall symptoms after intervention by 6 months, and maintained at 12 months. An improvement of >10 points was reported for fatigue, pain and insomnia in both arms. There were clinically unimportant differences post-baseline between groups for fatigue (p=0.055), pain (p=0.046) and dyspnoea (p=0.049).

Fagotti 2016 found most symptoms improved in both arms except for nausea and vomiting, which deteriorated by >10 points (p=0.047). In the primary debulking surgery group, a clinically meaningful improvement was present for appetite loss at $6^{th}$ cycle of chemotherapy. In the neoadjuvant chemotherapy group, fatigue, pain, dyspnoea, and insomnia improved >10 points by the $6^{th}$ cycle of chemotherapy, maintained at 6 months follow-up (Appendix-S6, page 49). On the QLQ-OV28 scale, peripheral neuropathy, hormonal symptoms and body image were worse by >10 points at the $6^{th}$ cycle of chemotherapy. While most symptoms subsided by 6 months, peripheral neuropathy and hormonal/menopausal symptoms persisted.

Soo Hoo et al (Soo Hoo et al., 2015) found only scores for peripheral neuropathy, body image, hormonal symptoms and diarrhoea had >10 points difference at 6 months. Hormonal symptoms worsened in both surgical groups (>10 points) with a 14 point difference at 9 months post-surgery. Statistical significance was not reported.

## Discussion:

**Main findings:** We found sparse evidence on the quality of life of women following ovarian cancer surgery. There were no important differences in the quality of life of patients in 3 randomised controlled trials comparing primary debulking surgery with neoadjuvant chemotherapy with improvements over baseline at 6 and 12 months but with evidence of selection bias, many missing data and substantial loss to follow-up. Only one observational study report results in the immediate postoperative period where differences in quality of life and symptom burden might be expected. Patient populations and baseline quality of life varied, with heterogeneous results, particularly up to 6 months: one single centre randomised controlled trial (Fagotti et al., 2016) selected patients with high tumour load using laparoscopy screening before randomisation, with lower median age and higher complete and optimal cytoreduction rate, with all patients in the primary debulking surgery arm undergoing maximal resection with higher reported morbidity. Even in this study, there was no difference in the quality of life at 6 months.

Regarding the quality of life after extensive surgery, two observational studies of unclear or poor quality showed clear evidence of confounding. A prospective study reported worse quality of life scores immediately after extensive surgery with an improvement by 9 months after, comparable to that in those who had standard surgery (Soo Hoo et al., 2015). Due to sample size, differences in the clinical characteristics and loss to follow-up, the data need to be interpreted with caution. A further observational study also has substantial limitations, lacking a baseline assessment and, as the patient selection was based on laparoscopic findings, applicability to patients selected by other means is unclear (Angioli et al., 2013).

Based on the limited available data, results show that patients undergoing extensive surgery appeared to tolerate the procedure and chemotherapy well as reflected by the comparable quality of life scores in all domains and the majority of their symptoms start to return to baseline or show improvement after 6 months post-surgery. Patients having neoadjuvant chemotherapy showed early improvement which may be due to the need for less extensive surgery and fewer morbidity, however, the exact explanation for this remains unknown.

**Strengths and limitations:** Although the review used robust methods, limitations lie in the quality and quantity of included studies. There was no randomised controlled trial specifically addressing quality of life in women undergoing extensive surgery: the observational studies do not provide evidence of sufficient quality or quantity. This is important given the evolution of surgical practice in advanced ovarian cancer. An inevitable concern with poor response rates in this patient population is that those most ill may not have returned quality of life questionnaires.

Extensive surgery frequently requires upper abdominal surgery that may involve liver mobilisation, liver resection, diaphragmatic stripping/resection, splenectomy, cholecystectomy, single or multiple bowel resections with adverse impact on the quality of life. Even so, surgical outcomes at 6 and 12 months may be confounded by chemotherapy. Despite many patients having received bowel resection, two trials only used a generalised instrument, EORTC QLQ-C30 to measure the quality of life without any specific instrument for ovarian cancer, stoma care, urological function and psychological stress due to fear of recurrence. More subtle ovarian specific differences between primary debulking surgery and neoadjuvant chemotherapy may not have been identified in the current research. The impact on sexual function is

also not known despite its inclusion on the OV28 questionnaire, as a measurement tool for this domain is not validated for use.

**Interpretation:** This is the first systematic review on quality of life in relation to surgery in advanced ovarian cancer. This review summarises the current understanding of quality of life in patients having either primary debulking surgery or neoadjuvant chemotherapy, but the comparative quality of life remains unknown for patients undergoing more extensive compared to standard surgery. There is little evidence on which symptoms are most prominent in women undergoing extensive surgery and what supportive measures might help. A high and potentially biased loss to follow-up means that the available data on quality of life following primary debulking surgery and neoadjuvant chemotherapy should be applied in clinical practice only with significant reservations.

**Conclusions:** Achieving no residual disease at the surgery has been associated with improved survival; however, this is confounded by the extent of baseline disease and the patient's perspective is important. A clear knowledge of survival gain weighed against the expected quality of life after intervention would help the patient to make an informed choice as some patients may value survival gains that adversely impact on their quality of life less than other patients. There is however little evidence to inform patients.

More research is needed to inform patients of the impact of extensive surgery on their expected quality of life in the light of potential gain in survival. This research should assess the quality of life at appropriate time points, using meaningful instruments capable of capturing the impact on patients appropriate for interventions

applied without overburdening the patient. The research should also focus on methods of minimising missing data. "Surgery in advanced Ovarian Cancer: Quality of life Evaluation Research-2 (SOCQER-2)" is a prospective multicentre study from the UK, Australia and India, aiming to report on patient reported outcomes (clinicaltrials.gov, 2015).

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**Author's contribution and disclosure statement:** SK, JL, SS and CC conceived the study. SK wrote the first draft. JL contributed as a 2nd reviewer. SS and CC supervised the protocol and the systematic review process. STK edited the final manuscript and all authors read and approved the final manuscript. The authors (SK, JL, STK and SS) declare that they have no competing interests. CC reports grants from the National Institute for Health and Care Excellence. STK reports other payments for lectures from Roche, other from Astra Zeneca, outside the submitted work.

Acknowledgements: Sue Bayliss – Assistance with electronic search strategy.

# Appendix S1: Electronic search strategy

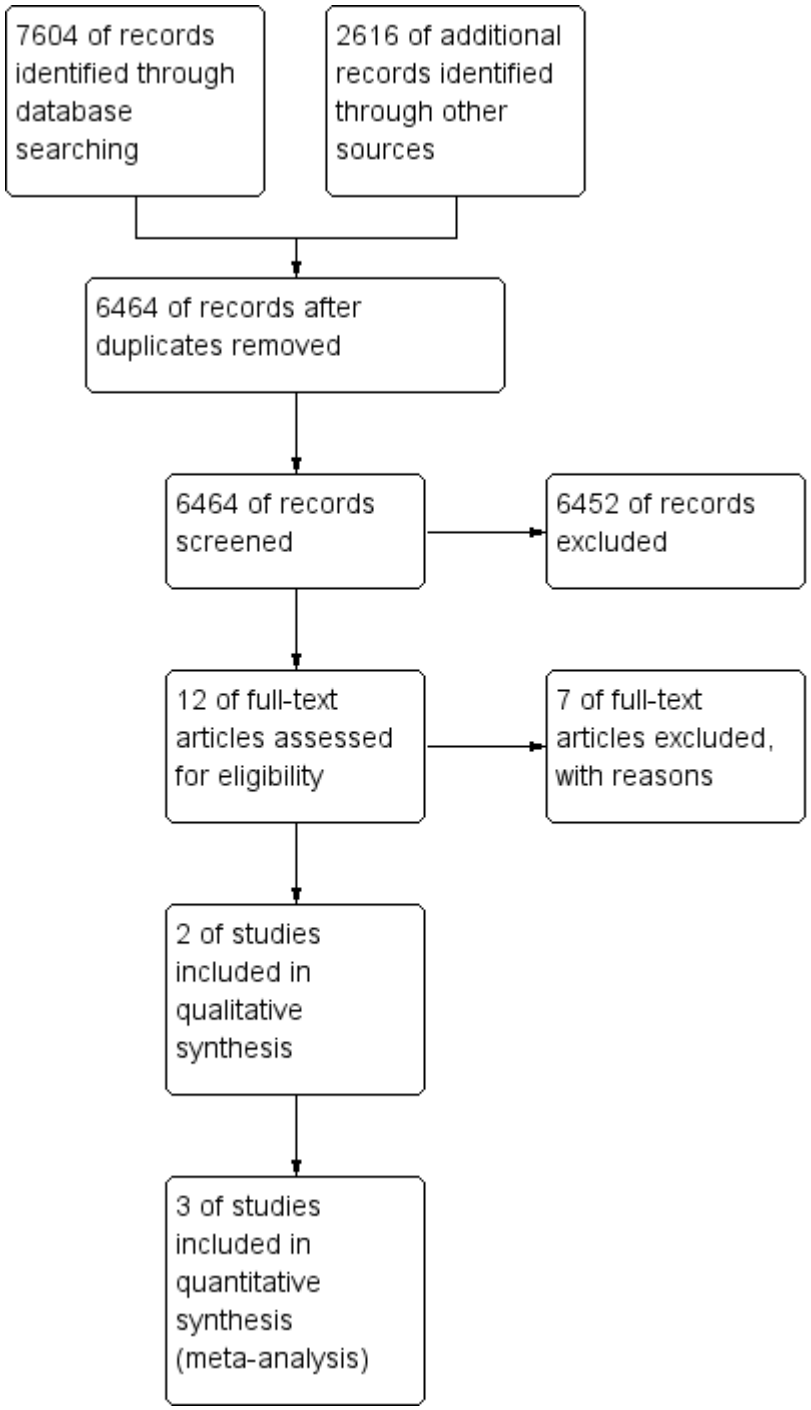
Sample search strategies for MEDLINE and EMBASE are given below.
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present and EMBASE 1974 to 2018 March.

1 exp Ovarian neoplasms/
2 (ovar* adj5 (cancer* or carcinom* or malignan* or neoplas*)).ti,ab.
3 1 or 2
4 Surg*.ti,ab.
5 (cytoreduc* or debulk*).ti,ab.
6 exp general surgery/
7 4 or 5 or 6
8 3 and 7
9 exp quality of life/
10 Quality of life.ti,ab.
11 QoL.ti,ab.
12 Self report/ or outcome assessment/ or patient satisfaction/ or "surveys and questionnaires"/ or treatment outcome/
13 exp "Outcome Assessment (Health Care)"/
14 (outcome* adj3 assess*).ti,ab.
15 Patient reported outcome.mp. or patient reported outcome.ti,tw,ab. or patient reported outcomes.ti,tw,ab
16 9 or 10 or 11 or 12 or 13 or 14 or 15
17 8 and 16

**CENTRAL:**

#1. Ovarian neoplasms
#2. (ovar* adj5 (cancer* or carcinom* or malignan* or neoplas*)) .ti,ab.
#3. #1 or #2
#4. Surg*.ti,ab.
#5. (cytoreduc* or debulk*) .ti,ab.
#6. General surgery
#7. #4 or #5 or #6
#8. #3 and #7
#9. Quality of life
#10.Patient reported outcome*
#11.Quality of life.ti,ab.
#12.Patient reported outcome.mp. or patient reported outcome.ti,tw,ab. or patient reported outcomes.ti,tw,ab.
#13. #9 or #10 or #11 or #12
#14. #8 and #13

## Appendix S2: Flow diagram of selection of studies



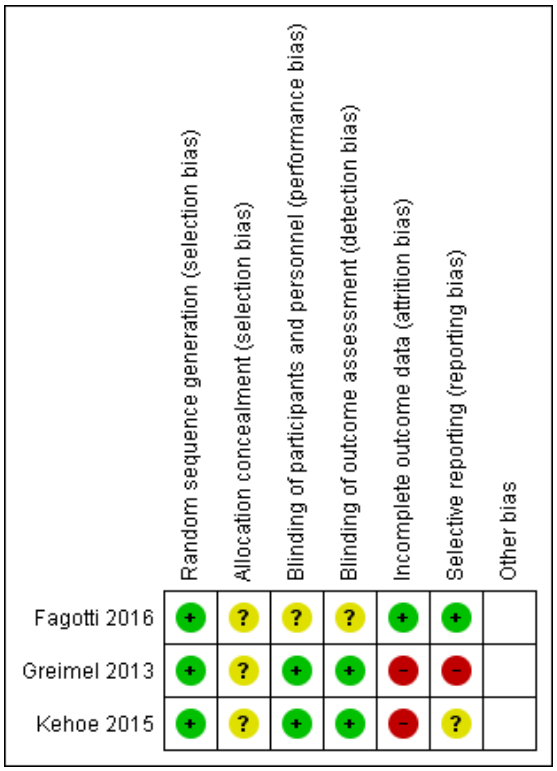
# Appendix S3: List and reasons for excluded studies

| Study | Reasons for exclusions |
|---|---|
| Von Hugo 1989 | Abstract was not available, therefore full text reviewed. The study was retrospective and based on telephonic interview of patients, relatives or doctors, if patients were not alive. (von Hugo et al., 1989). |
| Pfleiderer 1995 | Abstract was not available, therefore full text reviewed. Paper described different gynaecological and breast surgery (Pfleiderer, 1995). |
| Chan 2001 | Study included all gynaecological cancers & different treatments and included all stages. No subgroup analysis was performed according to cancer types or FIGO stages (Chan et al., 2001). |
| Greimel 2002 | Study included breast and gynaecological cancer sites and all stages. Number of ovarian cancer patients with stage III & IV provided but analysis of QoL outcomes did not report them separately (Greimel et al., 2002). |
| Chan 2003 | The study enrolled 17 patients for NACT followed by surgery, and 13 of them underwent debulking surgery. Optimal debulking was defined as residual disease of <2 cm. The data shows pattern of improvement in QoL score (QLQ-C30), but actual data scores are not provided. The study also compared the QoL scores to the conventional treatment (Chemotherapy only) from historic control (Chan et al., 2003). |
| Le 2004 | The study included patients with recurrent or progressive ovarian cancer and 52% of the patients previously had optimal surgical resection. FACT-O tool was used for QoL assessments, and mainly the effects of different types of chemotherapy were assessed (Le et al., 2004). |
| Brotto 2016 | No Pre-surgical baseline. Randomisation to different arms of chemotherapy after 4-6 weeks after primary surgery. Some patients had interval surgery after randomisation to the study. A large number of patients did not have surgery. FIGO stage IIB - IV included in the study. Data according to stratification by surgery not available (Brotto et al., 2016). |

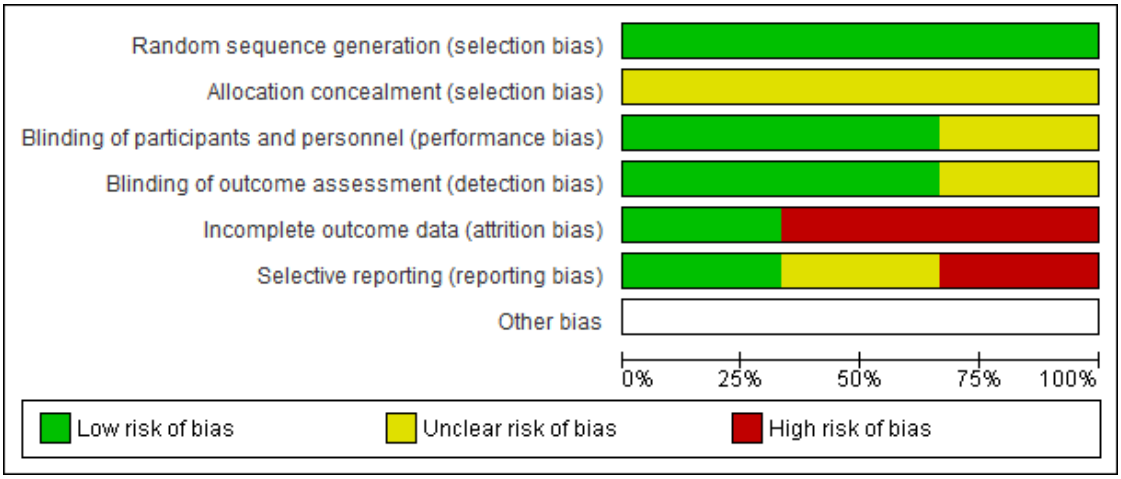
FIGO = International Federation of Gynaecology and Obstetrics, QoL = Quality of life, NACT = Neoadjuvant chemotherapy, QLQ-C30 = EORTC Quality of Life questionnaires for cancer patients, FACT-O = Functional Assessment of Cancer Therapy–Ovarian

# Appendix S4: Risk of bias in included randomised controlled trials

A. Risk of bias summary: review authors' judgements about each risk of bias item for included RCTs




B. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included RCTs.



# Appendix S5: Risk of bias in observational studies: Newcastle - Ottawa quality assessment scale

| Domains | Angioli 2013 | Author's judgement | Soo Hoo 2015 | Author's judgement |
|---|---|---|---|---|
| **Selection** | | | | |
| **Representativeness of the exposed cohort** | Highly selected group of users, not truly representative of the average advanced ovarian cancer patients in the community | High risk | Truly representative of the average advanced ovarian cancer patients in the community | Low risk |
| **Selection of the non-exposed cohort** | Drawn from the same community as the exposed cohort | Low risk | Drawn from the same community as the exposed cohort | Low risk |
| **Ascertainment of exposure** | Secure record | Low risk | Secure record | Low risk |
| **Demonstration that outcome of interest was not present at start of study** | Yes, but no baseline data available | High risk | Yes | Low risk |
| **Comparability** | | | | |
| **Comparability of cohorts on the basis of the design or analysis** | Study controls for the type of surgery patients received with predefined criteria as standard surgery and extensive upper abdominal surgery, However standard surgery group had high proportion of early stage disease | High risk | Study controls for the type of surgery patients received with predefined criteria as standard surgery and extensive upper abdominal surgery, However standard surgery group had high proportion of early stage disease | High risk |
| **Outcome** | | | | |
| **Assessment of outcome** | Self-report | Low risk | Self-report | Low risk |
| **Was follow-up long enough for outcomes to occur** | No | High risk | Baseline to 9 months post-surgery | Low risk |
| **Adequacy of follow up of cohorts** | Complete follow up - all subjects accounted for, but only at single point after completion of treatment. | High risk | Follow up rate at end of study period was approximately 50%, but no description of those lost were documented | High risk |

# Appendix S6: QLQ-C30 – Symptom scale

| | | Primary surgery | | | | | NACT | | | | | p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **QLQ-C30** | | **0** | **6 months** | **12 months** | **Points change at 6 months** | **Points change at 12 months** | **0** | **6 months** | **12 months** | **Points change at 6 months** | **Points change at 12 months** | |
| **Fatigue** | A | 46.2 | 29.0 | 29.1 | -17.2 | -17.1 | 40 | 25.7 | 29.1 | -14.3 | -10.9 | **0.055** |
| | B | 42.9 | **50.0** | 32.0 | 7.1 | -10.9 | 52.2 | 39.9 | 34.3 | - 12.3 | -17.9 | **0.471** |
| **Nausea/vomiting** | A | 12.3 | 3.2 | 3.4 | -9.1 | -8.9 | 12.7 | 4.2 | 5.6 | -8.5 | -7.1 | **0.753** |
| | B | 20.1 | **47.8** | **30.8** | **27.7** | **10.7** | 19.1 | **31.1** | **34.3** | **12** | **15.2** | **0.047** |
| **Pain** | A | 36.7 | 19 | 19.1 | -17.7 | -17.6 | 29.9 | 15.4 | 15.1 | -14.5 | -14.8 | **0.046** |
| | B | 30.5 | 21.4 | 10.5 | -9.1 | -20 | 26.5 | 14.5 | 14.9 | -12 | -11.6 | **0.155** |
| **Dyspnoea** | A | 22.9 | 16.8 | 15.6 | -6.1 | -7.3 | 27.9 | 16.3 | 18.9 | -11.6 | -9 | **0.049** |
| | B | 37.8 | 35.7 | 15.2 | -2.1 | -22.6 | 33.7 | 16.2 | 20.7 | -17.5 | -13 | **0.013** |
| **Insomnia** | A | 43.1 | 26.4 | 24.8 | -16.7 | -18.3 | 37.6 | 27.2 | 22.1 | -10.4 | -15.5 | **0.112** |
| | B | 47.7 | 46.5 | 17.9 | -1.2 | -29.8 | 38.9 | 25.8 | 17.5 | -13.1 | -21.4 | **0.024** |
| **Appetite loss** | A | 42.9 | 9.3 | 9.6 | -33.6 | -33.3 | 39.1 | 9.5 | 10.6 | -29.6 | -28.5 | **0.208** |
| | B | 45.8 | 35.1 | 23.8 | -10.7 | -22 | 42.2 | 28.5 | 24.6 | -13.7 | -17.6 | **0.126** |
| **Constipation** | A | 26.1 | 17.9 | 12.5 | -8.2 | -13.6 | 24.8 | 13.2 | 14.2 | -11.6 | -10.6 | **0.455** |
| | B | 31.8 | **38.5** | **41.0** | 6.7 | 9.2 | 33.2 | 26.6 | **41.4** | -6.6 | 8.2 | **0.109** |
| **Diarrhoea** | A | 20 | 4.1 | 4.7 | -15.9 | -15.3 | 17.9 | 9.4 | 8.1 | -8.5 | -9.8 | **0.053** |
| | B | 13.2 | 13.9 | 14.0 | 0.7 | 0.8 | 13.0 | 6.5 | 7.1 | -6.5 | -5.9 | **0.202** |
| **Financial difficulties** | A | 8.3 | 11.7 | 12.4 | 3.4 | 4.1 | 10.4 | 10.2 | 10 | -0.2 | -0.4 | **0.341** |
| | **B** | **39.8** | **43.9** | **33.0** | **4.1** | **-6.8** | **28.6** | **37.7** | **39.5** | **9.1** | **10.9** | **0.466** |

A = Greimel 2013, B = Fagotti 2016, QLQ-C30 = EORTC Quality of Life questionnaires for cancer patients

# Appendix S7: PRISMA statement and checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| **Title** | 1 | Identify the report as a systematic review, meta-analysis, or both. | Title page |
| **ABSTRACT** | | | |
| **Structured summary** | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 1 - 2 |
| **INTRODUCTION** | | | |
| **Rationale** | 3 | Describe the rationale for the review in the context of what is already known. | 3 |
| **Objectives** | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3 - 4 |
| **METHODS** | | | |
| **Protocol and registration** | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 5 |
| **Eligibility criteria** | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4 |
| **Information sources** | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4 |
| **Search** | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | AppendixS1 |
| **Study selection** | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4, Appendix S2 |
| **Data collection process** | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 4 |
| **Data items** | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 4 |
| **Risk of bias in individual studies** | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 4, Appendix S4, S5 |
| **Summary measures** | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 3, Protocol |
| **Synthesis of results** | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 4, Protocol |
| **Risk of bias across studies** | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | Appendix S4, S5 |
| **Additional analyses** | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | NA |
| **RESULTS** | | | |
| **Study selection** | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 4, Appendix S2, S3 |
| **Study characteristics** | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Table 1 |
| **Risk of bias within studies** | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Appendix S4, S5 |
| **Results of individual studies** | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Figure 1 |
| **Synthesis of results** | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 5, Protocol |
| **Risk of bias across studies** | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Appendix S4, S5 |
| **Additional analysis** | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | NA |
| **DISCUSSION** | | | |
| **Summary of evidence** | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 9 - 10 |
| **Limitations** | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 9 - 10 |
| **Conclusions** | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 10 – 11 |
| **FUNDING** | | | |
| **Funding** | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | Title page, Protocol |

# CHAPTER 3:
# SURGERY IN ADVANCED OVARIAN CANCER: QUALITY OF LIFE EVALUATION RESEARCH (SOCQER-2)


## Abstract:

**Objectives:** Extensive surgery has been shown in retrospective studies to improve survival from advanced ovarian cancer. The uptake of extensive surgery in the UK has been variable, owing to concerns regarding the impact on Quality of life (QoL) and organisational factors. Thus, utilization of procedures contributing to high/intermediate surgical complexity score (SCS), for similar preoperative disease load, varies across centres in the UK. We investigated QoL and outcomes after surgery for first line treatment of advanced ovarian cancer, in parallel, multicentre, prospective cohorts across 12 centres in the UK and one centre in India.

**Methods:** Patients completed EORTC QLQ-30, OV28, CR29 (non-stoma or stoma subset) at preoperative, 6 weeks, 6, 12, 18 and 24 month postoperative time-points. SCS, intraoperative disease load and survival data were collected. For Kaplan Meier survival analyses, patients were censored at two years or at date lost to follow-up. Cox proportional hazard models of overall survival were produced using a forward stepwise procedure. EORTC QLQ-C30 global scores at 6 weeks, 6 months and 12 months post-surgery contributed to general linear repeated measures models (SPSS 24).

**Results:** Patients undergoing low, intermediate and high SCS procedures had substantially different characteristics, for example, younger patients with better performance status and lower comorbidities were selected for more extensive

surgeries. 70% of patients received NACT and 30% underwent primary debulking surgery. All groups included patients with a high burden of disease. Progression free and overall survival was poorer with residual disease in all three groups following surgery (log-rank p=<.001). Age-Adjusted Charlson Comorbidity Index, pre-operative albumin and Peritoneal Carcinomatosis Index were independent predictors of survival. QoL in domains of EORTC QLQ-C30 and OV28 improved within all groups by 6 – 12 months post-surgery (p<.001), however physical function and emotional function took longer to recover in the high SCS group. Fatigue was reported worse for high SCS patients, and insomnia was reported worse for patients with residual disease. All groups of patients reported peripheral neuropathy as a persisting symptom even beyond 12 months post-treatment. However, there were no statistically or clinically significant differences between study groups.

**Conclusions:** QoL of patients in most categories showed improvement over baseline by 12 months, with no association with surgical complexities. Extensive surgery (high SCS) does not decrease patients' QoL compared to preoperative scores. The utilization of extensive surgery to achieve complete cytoreduction for high disease load is associated with improved survival and no deleterious impact on QoL.

## Introduction:

Overall survival (OS) and progression free survival (PFS) are critical outcomes for cancer patients; however quality of life is of fundamental importance to patients (Bottomley, 2002). Health related Quality of life (HRQoL) is considered just as important as survival in making treatment decisions (Osoba, 1994, Young and Maher, 1999). Standard treatment of advanced ovarian cancer (stage III and IV) comprises a combination of cytoreduction surgery and chemotherapy (Ozols et al., 2003, Jayson et al., 2014, Clamp et al., 2017). Multiple studies have shown improved PFS and OS with complete cytoreduction of disease at surgery, leading to the introduction of more extensive surgical procedures to achieve this goal (Eisenkop et al., 1998, Eisenhauer et al., 2006, Aletti et al., 2006, Chi et al., 2009, Elattar et al., 2011). However, the initial disease burden still remains a significant prognostic indicator for survival despite achieving complete cytoreduction (Horowitz et al., 2015). In addition, considerable variations exist in international surgical opinion and practice (Eisenkop and Spirtos, 2001, Cibula et al., 2011, Brand, 2011, Barton et al., 2013, Naik et al., 2016). A Cochrane review concluded that there is only low quality evidence with regards to survival outcomes (PFS and OS) of extensive surgery as compared to standard surgery. The authors suggested that extensive surgery may improve overall survival, but the effect on progression free survival, morbidity and quality of life (QoL) after surgery are not clear (Ang et al., 2011).

The morbidities associated with extensive surgeries are, not surprisingly, higher (Kuhn et al., 1998, Chi et al., 2010) but there is a lack of evidence on patient reported outcomes (PRO) after such procedures. Understanding PRO after extensive surgery for ovarian cancer is particularly critical given three factors: the

absence of RCT data to support utilisation of extensive surgery; the challenge in robustly estimating the survival benefit for any individual patient from extensive surgery; and the putative survival gain from extensive surgery which could be hypothetically offset by the deterioration in QoL as a result of increased morbidity. Data from two randomised control trials (RCT) comparing primary debulking surgery (PDS) versus neoadjuvant chemotherapy (NACT) found that survival in patients receiving NACT was not inferior to those receiving PDS [HR 0.93 (CI 0.82 – 1.05), p=0.376] but overall morbidity was reduced with the use of NACT (Kehoe et al., 2015). The systematic review of QoL following surgery in advanced ovarian cancer (Chapter 2) did not show a difference in the QoL of patients either having PDS or NACT (Kumar et al., 2019). However, it found that, this information could potentially be confounded due to heterogeneity and major attrition bias in included studies. There was insufficient data reporting QoL after extensive surgery for advanced ovarian cancer.

To report on QoL after extensive surgery compared to standard surgery, SOCQER-1 evaluated PRO and reported that the investigation of QoL post-surgery was feasible and acceptable to patients (Soo Hoo et al., 2015). Extensive surgery was associated with poorer QoL at 6 weeks to 3 months when compared with standard surgery, but there was no significant difference in QoL by 6 to 9 months after surgery. However, this was a single centre pilot study with a limited number of participants and there was a considerable difference in the patient characteristics between the groups. As such this information is critical to patients and health care providers: the National Institute for Health and Care Excellence (NICE, UK) commissioned “Surgery in Ovarian Cancer: Quality of life Evaluation Research

(SOCQER-2)" as a larger multicentre exploratory prospective cohort study to evaluate data on prospective multicentre outcomes after extensive surgery for ovarian cancer, including patients' QoL. The finding is proposed to inform the revision of NICE Interventional Procedure Guidance [IPG-470] (NICE, 2013).

The SOCQER-2 is a multicentre, prospective, exploratory, observational cohort study, recruited patients with advanced ovarian cancer from 12 centres across the United Kingdom from September 2015 to September 2016. Two other centres at Melbourne (Australia) and Kolkata (India) also collaborated by running a parallel study based on the same protocol, but with separate ethical approval. In this thesis, I have presented results from the UK and Kolkata centres.

## Aims:

The primary aim was to evaluate QoL and progression free survival of patients having debulking surgeries for advanced ovarian cancer with different extensiveness or complexity of surgery using EORTC QoL questionnaires QLQ-C30 and EORTC QLQ-OV28. Further exploration into postoperative morbidities, overall survival and assessment of QoL was also performed based on the timing of debulking surgery, disease load present at the surgery and residual disease status using EORTC QLQ-C30 and QLQ-OV28.

## Hypothesis:

The hypothesis underlying the study was derived from our observations from the SOCQER 1 study. We hypothesised that patients undergoing high SCS would have worse QoL postoperatively and that any differences between the two groups would not be apparent by 12 months post-surgery. Any benefits from extensive surgery in

removing disease load may manifest in later months up to 24 months postoperatively.

## Methods:

**Study design and participants:** SOCQER-2 is an international, multicentre, prospective, observational cohort study. The primary aim of the study is to describe PRO for patients with advanced ovarian cancer undergoing different types of cytoreductive surgery. Participants were recruited from 12 centres across the UK and a centre in Kolkata (India). The centres varied in routine utilisation of extensive surgical procedures for advanced ovarian cancer. All participants were identified prior to surgical treatment and data collection planned at regular intervals for follow up after surgery up to 24 months or until the progression of their disease or death.

### Inclusion criteria:

- Patients with suspected or confirmed ovarian cancer with macroscopic spread beyond the pelvis (FIGO stage III-IV), determined through pre-operative clinical assessment or imaging (this included those having fallopian tube or peritoneal cancer).
- Patient listed for PDS or NACT with the intent of delayed debulking surgery.

### Exclusion criteria:

- Ovarian, fallopian tube or primary peritoneal cancer not confirmed to be FIGO stage 3 – 4 post-surgery.
- Ovarian, fallopian tube or primary peritoneal cancer relapse.
- Not ovarian, fallopian or primary peritoneal cancer at histology.

- Progression of cancer.
- Informed consent not obtained.
- Primary chemotherapy with no intention of surgery.
- Actively receiving treatment for another cancer.
- Secondary cancers in less than 5 years or relapsed secondary cancer in the past.
- If a patient did not have debulking surgery or was deemed inoperable after consent.

**Data collection:** The data collection was planned in 2 components: clinical data, including demography and details of intervention to be reported by the surgical team and patient reported outcomes data, to be reported directly by participants. Eligible patients, who were suspected to have macroscopic disease beyond pelvis (ovarian, fallopian tubes or peritoneal cancer), were identified at multi-disciplinary team meetings. Patients were then approached by principal investigators or assigned research nurses for recruitment and consent at clinics prior to the surgery. Clinical characteristics of recruited patients were captured using Case Report Forms (CRF). The schematic representation of clinical data and PRO data collection plan is provided in Figure 2.

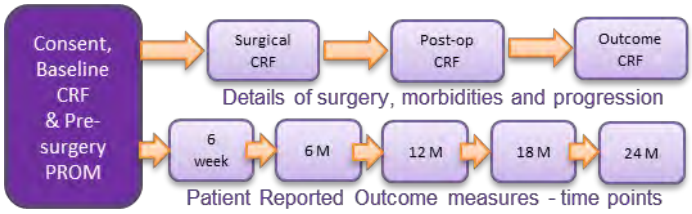



**Figure 2: Schematic representation of data collection plan; CRF: Case report forms, PROM: Patient reported outcome measures, M: Months.**

**Clinical data:** CRFs were designed to collect data related to surgical outcomes and agreed with all principal investigators and steering group committee members. Where possible, standardised and validated data capture tools were used as described under "Scientific instruments for clinical data collection" below. The baseline CRF was completed at the time of consent to participate in the SOCQER-2 study and included the demographic details of the patient, their medical history and details of the treatment plan along with reasons for selecting patients for NACT (Appendix SQR1, page 137). The surgical CRF meticulously explored the details of the operating team, operating timing, disease response to pre-operative chemotherapy, disease load at surgery, types of surgical cytoreduction, outcome of cytoreductive surgery, any complications encountered during surgery, time consumed during the procedure and reasons for any residual disease (Appendix SQR2, page 139). Disease load at the beginning and end of surgery was carefully compared with types of cytoreduction surgery performed as a part of our quality assurance. The postoperative CRF mainly collected data on patient's recovery, any complications up to 6 weeks using the Clavien-Dindo classification and details of post-operative chemotherapy (Appendix SQR3, page 146). The outcome CRF was

used to collect data on the status of participants at 18 months or at disease progression, defined by either clinical assessment, rise in CA125 or radiologically (Appendix SQR4, page 148). The AKI CRF was particularly designed to investigate the incidence of acute kidney injury (AKI) as a part of our specific morbidity enquiry during the treatment of ovarian cancer, which had not been previously explored in the context of ovarian cancer surgery. It captured data on associated risk factors and changes in renal function tests during treatment (Appendix SQR5, page 150) and reported separately as chapter 4.

Health Research Authority ethical approval was obtained (Solihull National Health Service Research Ethics Committee reference number 15/WM/0124), as was NHS approval from participating UK sites. Equivalent approvals were obtained locally for the parallel studies in Australia and Kolkata.

SK and JL visited a few centres for site initiation and provided training to staff collecting data, while other site initiations were carried out using Skype audio-visual communication. Each centre captured data prospectively using either paper based CRFs or web-based CRFs at baseline, after surgery, 6 weeks post-surgery and at 18 months post-surgery (or at the time of progression, death or withdrawal from study). AKI CRFs were completed 6 months after the surgery by a designated trainee at each centre as all patients were anticipated to have completed their treatment cycle by then. All centres were advised to recruit consecutive patients to minimise selection bias and a screening log was maintained.

The electronic database platform: The REDcap system is easy to use, secure data capture tool for building online databases (Harris et al., 2009) and has been

extensively used for different types of research in more than 900 institutions worldwide. It is a web based software tool developed at Vanderbilt University at Tennessee, USA and enables designing and developing an electronic database. The software permits the user to define data elements, create and edit data points and transfer the data in the form of spreadsheets, reports and also communicates with various types of statistical software. Training and educational materials are available online and also incorporated within the software. Each user's access is governed by the providing institution. In our research, each centre provided a list of GCP trained users who were given access to the REDcap system with their unique login details. Any editing and change in the data were recorded in real time. The data were centrally monitored by two trained staff (SK & JL) at University of Birmingham (UOB) and any queries were satisfied by centres to ensure relevance and quality of data. While most of the centres completed the data online, a few centres choose to complete the data on paper based CRFs, which were sent to UOB for quality checks and transfer to the REDcap system. SK designed the electronic format of all clinical CRFs with the help of a senior research fellow (GR) at UOB.

**Scientific instruments for clinical data collection:** The study was not designed to use any intervention in the management of patients with advanced ovarian cancer; rather, the aim was to capture the variations in practice and use of different types of surgeries. Further information on cancer centre practice and case load was requested for the duration of study and consent was obtained for linkage of patient's data with the Cancer Outcomes and Services Dataset (COSD) to understand the denominator data for utilisation of treatment methods used and overall survival (Not

discussed in this thesis). The clinical data collection utilised various scientific tools to describe participant's characteristics, disease load, surgical interventions and its outcomes.

1. ***Performance status (PS):*** The importance of performance status in describing the general well-being of patients has been identified since 1948 and has been used to identify patient's suitability for treatment (Karnofsky et al., 1948). Its association with survival and QoL is well known in cancer patients (Mol et al., 2016). In 1960, Eastern Co-operative Oncology Group (ECOG) adapted this and provided a simpler version, later converted to 6 point scale, and also known as WHO Performance status or ECOG performance status (Figure 3) (Oken et al., 1982). The scale is designed to express the physical functioning of a cancer patient and has been validated for use, however subjective differences in rating the score do exist (Mor et al., 1984, Buccheri et al., 1996). In SOCQER-2, this tool was used to identify patient's physical fitness and also to understand potential bias in patient selection for surgery. A patient with better physical fitness may demonstrate a low disease burden and a better ability to sustain surgical intervention and chemotherapy related effects, therefore, this data could be assessed for its prognostic value for survival and QoL outcomes through multivariate analysis (Figure 3).

| ECOG | Description |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on selfcare. Totally confined to bed or chair |
| 5 | Dead |

Figure 3: ECOG Performance Status

2. ***Age-adjusted Charlson Comorbidity Index (ACCI):*** The Charlson Comorbidity Index (CCI) was proposed and validated for use in clinical practice, mainly to predict 1 year mortality and resource use based on the International Classification of Disease (ICD) diagnosis codes as per hospital administrative data. A 19 item list of comorbidities were presented with weighted score (range 1-6, , RR <1.2 = weight 0, RR ≥ 1.2 but <1.5 = weight 1, RR ≥ 1.5 but <2.5 = weight 2, RR ≥ 2.5 but <3.5 = weight 3, and for 2 conditions - metastatic solid tumour and AIDS = weight 6), and the sum of these scores presented as CCI, where 0 would mean no comorbidity and a higher score would define an increase in morbidities or its severity (Charlson et al., 1987). It was demonstrated that with each increased level of comorbidity index, cumulative mortality attributable to comorbidities increased in a stepwise manner. Age was also found as an independent predictor of mortality in the longer follow up. Later, with 2 subcategories, it was reduced to a 17 item index (Deyo et al., 1992) and age was introduced as additional

factor and validated in another study. It was described that an increase in one comorbidity score was equal to an increase in the relative risk of mortality as if the increase was a decade of age (Charlson et al., 1994). The combined use of age and CCI has been favoured in many oncological studies and has recently been used in a cohort of ovarian cancer patients to predict resource use, postoperative morbidity, progression free survival and overall survival (Suidan et al., 2015, Kahl et al., 2017, Phillips et al., 2017). In SOCQER-2, ACCI was used to measure its association with patient selection for surgery, types and extent of surgical intervention, the outcome of the surgical intervention and morbidities (Figure 4). As performance status and ACCI may be surrogate markers for similar outcomes, it would be possible to identify which index has a better predictive value.

The ACCI needed to be modified by not using any score for metastatic tumour due to the nature of our study as also reported by Suidan, 2015 (Suidan et al., 2015). Patients with advanced ovarian cancer would have tumour with metastasis and therefore all patients would start with a minimum score of 6, which would be misleading in outcome assessment. All validated data items with scores were entered into the REDcap system to provide ACCI and also checked individually from the ACCI calculator (Hall et al., 2004).

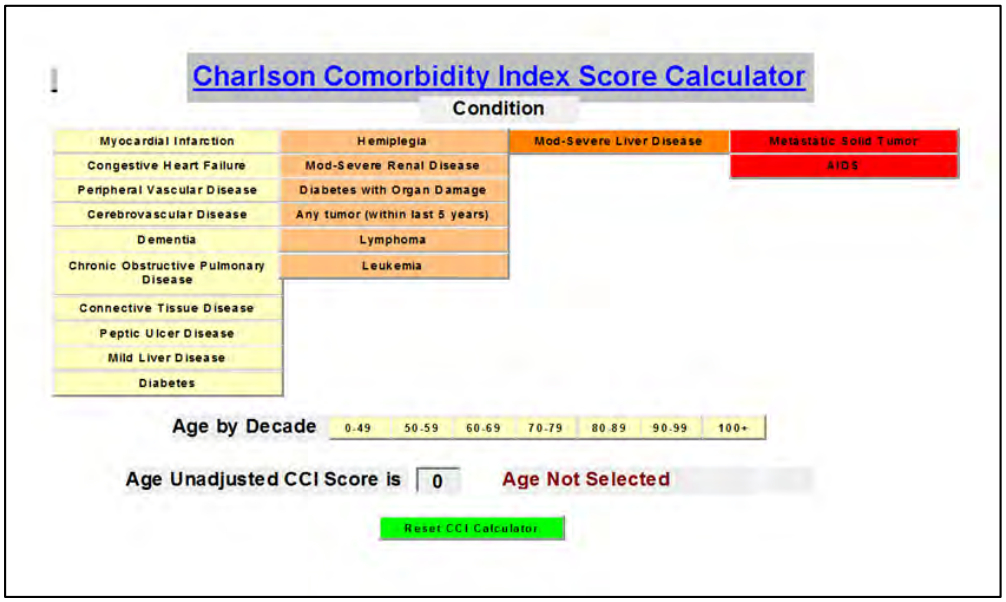



**Figure 4: Charlson Comorbidity Index Score Calculator with and without age adjustment (Ref: Hall, W. H., et al. (2004).**

3. ***Peritoneal Carcinomatosis Index (PCI):*** The primary evidence of peritoneal carcinomatosis as a prognostic marker is reported from colorectal and appendicular cancer surgeries (Sugarbaker and Jablonski, 1995, Jacquet P., 1996). If reported well, PCI provides a systematic approach towards assessing tumour location and volume prior to surgery and residual disease status as an outcome of surgery (Figure 5). Therefore, PCI has been used extensively in advanced ovarian cancer surgery to provide the details of initial tumour load, complexities of surgeries that may be required to achieve cytoreduction and postoperative residual disease status. It has also been utilised to predict resectability, morbidity and survival outcomes (Friedlander, 1998, Tentes et al., 2003, Gilly et al., 2006, Chereau et al., 2010, Llueca et al., 2018). Comparing PCI with other scoring methods [FIGO stage, Eisenkop score (Eisenkop et al., 2003), Aletti score (Aletti et al., 2007b), Fagotti score (Fagotti et al., 2006) and modified Fagotti score (Brun et al., 2008)] in

advanced ovarian cancer, PCI was a better predictor of resectability and survival while Aletti score was a better predictor for postoperative morbidity (Chereau et al., 2010). PCI reporting in our study was utilised for its ability to provide information on cancer load prior to surgery, so that in addition to identifying patients with higher disease burden, we could also assess the quality and extensiveness of surgical intervention reported. An assessment of post-operative PCI would provide information on the exact location and volume of residual disease. For example, if pre-operative PCI showed disease in upper abdomen, and postoperative PCI showed complete resection, the patient must have had a relevant procedure in that abdominal quadrant. In cases where there were any discrepancies observed, this was discussed with data provider team and therefore relevance and quality of the data was ensured (SK). In addition to the clinical information, the knowledge of PCI also provided insight into case selection for surgery in participating surgical centres.

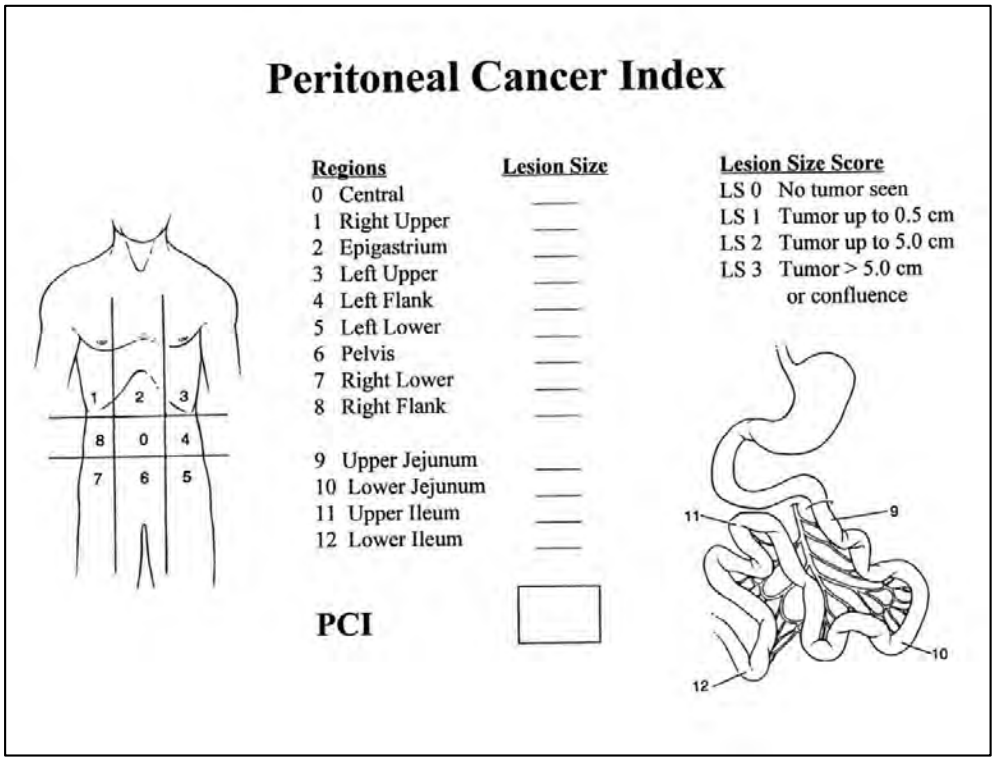



**Figure 5: Peritoneal cancer index (PCI). Sugarbaker P.H. (eds) Peritoneal Carcinomatosis: Principles of Management. Cancer Treatment and Research, vol 82. Springer, Boston, MA.**

4. ***Intra-operative Mapping of Ovarian cancer (IMO):*** A limitation of reporting the PCI score alone without details of location is that it may not represent complete information. For example, a score of 9 is equivalent to less than 5mm disease in 9 quadrants of abdomen and can also represent a pelvic tumour plus omental tumour plus another isolated nodule on mesentery or diaphragm. While the former case may not be resectable to nil residual disease, resection in the latter case is easily feasible. Therefore, PCI was complemented with another tool (SK), which could be easily derived, from PCI table to show the level of disease as described by Sehouli et al (Sehouli et al., 2003, Sehouli et al., 2009). The levels of disease are defined as: pelvic disease (Level 1), abdominal disease up to lower border of the stomach

(Level 2) and upper abdominal disease (Level 3) (Figure 6). The information from this type of classification enabled us to segregate patients with upper abdominal disease versus no upper abdominal disease and also informed us on residual disease location. In addition, this would also be used as a predictor for resectability, survival outcomes and a quality assessment tool for surgical centres.

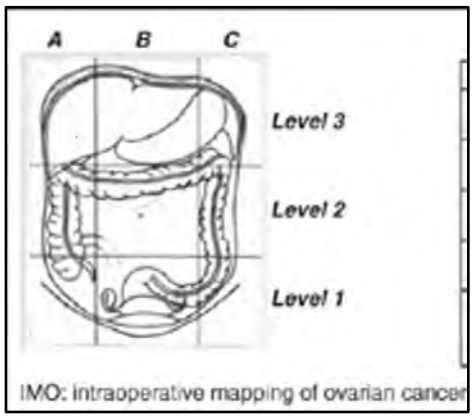



**Figure 6: Intraoperative mapping of ovarian cancer, Sehouli, J., et al. (2003).**

5. ***Alleti's Surgical Complexity Score (SCS):*** To stratify patient groups on the basis of types of cytoreduction surgery undertaken, we used Aletti's Surgical Complexity Score as it fits very well in our research context (Aletti et al., 2007a). It can identify patients based on the number and types of procedures with a defined score and has the least chance of inter-observer error. In addition, it has also been reliably used and validated as one of the most predictable tools for postoperative complications and survival outcomes in research (Aletti et al., 2007b, Chereau et al., 2010). A Surgical Complexity Score (SCS) is generated by summing the points for all procedures carried out. Surgery with a score of up to 3 is classed as low (standard surgery), a

score of 4-7 is classified as ‘intermediate’ and surgery with a score of 8 or above is classified as ‘high’ complexity. As Aletti’s surgical complexity does not cover a few additional procedures carried out in SOCQER-2 patients, two ovarian cancer surgeons (SK and SS) reviewed these procedures and classified them with an arbitrary higher score (Pancreatic tail resection, cholecystectomy, resection of disease from lesser sac and porta-hepatis – each scored 5 due to probability of higher morbidity). It was decided to review the effect of these scores during data analysis to find out if any patient changed their designated categories due to this modification. It was predicted to be unlikely, as these additional procedures are usually associated with higher complexity surgeries. Calculation of Aletti’s surgical complexity score with or without these modifications was planned and any differences in the outcome were planned to be reported. The Aletti’s scoring system is provided in Figure 7.

| Procedure | Points |
|---|---|
| TH-BSO | 1 |
| Omentectomy | 1 |
| Pelvic lymphadenectomy | 1 |
| Paraaortic lymphadenectomy | 1 |
| Pelvic peritoneum stripping | 1 |
| Abdominal peritoneum stripping | 1 |
| Rectosigmoidectomy_T-T anastomosis | 3 |
| Large bowel resection | 2 |
| Diaphragm stripping/resection | 2 |
| Splenectomy | 2 |
| Liver resection/s | 2 |
| Small bowel resection/s | 1 |

| Complexity score groups | Points |
|---|---|
| 1 (low) | 3 or fewer |
| 2 (intermediate) | 4-7 |
| 3 (high) | 8 or more |

*TH-BSO*, total hysterectomy-bilateral salpingo-oophorectomy.

**Figure 7: Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. Aletti et al, Am J Obstet Gynecol 2007a.**

6. ***Clavien-Dindo classification of postoperative morbidity:*** Post-operative complications are generally used as a measure to evaluate the outcomes of surgical procedure. However, the complications could be either related to the patient's characteristics or to the complexity of surgical procedures. Standardized reporting of post-operative complications is essential to compare results, quality measurement and could relate to the QoL after surgery. Clavien-Dindo classification of post-operative morbidity is a well

validated tool, and has been widely used in clinical practice (Dindo et al., 2004). The evidence base for this tool originated from the cohort of cholecystectomy patients (Clavien et al., 1992), and later on, it was validated in a large database from multicentre international group of surgical teams with some modifications in the context of a wider range of surgeries (Dindo et al., 2004, DeOliveira et al., 2006, Clavien et al., 2009). The reporting bias is minimal as the grading of complications is based on the therapy used to treat specific complications. Its use in ovarian cancer surgery is well known (Benedetti Panici et al., 2015, Kahl et al., 2017, Magge et al., 2017) and therefore, it provided us a sound platform to capture complications from multiple centres in our research.

The grading of morbidities (Dindo et al., 2004) is based on the therapy used to treat a complication. Grade 1 includes any deviation from the normal post-operative course without the need of pharmacological (exceptions allowed), surgical, endoscopic or interventional procedures. Grade 2 complications are those which require pharmacological treatments except for those allowed for grade 1 complication and include antibiotic treatment, blood transfusion, parenteral nutrition etc. Grade 3 complications include those requiring surgical, endoscopic or radiological intervention and further classified as 3a and 3b based on the use of general anaesthesia. Life threatening complications are classed as grade 4 and death of a patient is classed as grade 5 (Figure 8). A suffix “d” is added to any grade, if any disability has resulted from the complication. The detail of classification is provided below. All reported adverse events were graded by an ovarian cancer surgeon (SK)

as per Clavien-Dindo classification. In this thesis, we defined postoperative duration as up to 6 weeks period after surgery.

| Grade | Definition |
|---|---|
| Grade I | Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions |
| | Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside |
| Grade II | Requiring pharmacological treatment with drugs other than such allowed for grade I complications |
| | Blood transfusions and total parenteral nutrition are also included |
| Grade III | Requiring surgical, endoscopic or radiological intervention |
| Grade IIIa | Intervention not under general anesthesia |
| Grade IIIb | Intervention under general anesthesia |
| Grade IV | Life-threatening complication (including CNS complications)* requiring IC/ICU management |
| Grade IVa | Single organ dysfunction (including dialysis) |
| Grade IVb | Multiorgan dysfunction |
| Grade V | Death of a patient |
| Suffix "d" | If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication. |

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

**Figure 8: Dindo, D., et al. (2004). "Classification of surgical complications**

**Patient reported outcome (PRO) data:** QoL data or patient reported outcome measures (PROM) were collected using European Organizations for Research and Treatment of Cancer (EORTC) tools in combination with other specific tools, designed to report on general well-being, and also addressing specific issues such as psychological health and fear of recurrence. Patients were offered the option of completing PROM instruments either using paper based forms or online. If choosing the online option, patients used online software called Q-tool, developed by Leeds University to collect PROM from survivors with cancer in the ePOCS study (electronic Patient-reported Outcomes from Cancer Survivors) (Ashley et al., 2013). Q-tool collects the questionnaire data and stores it securely behind the Leeds University firewall. Importantly, Q-tool does not contain any patient identifiable data. SK and JL received training to use Q-tool at Leeds. It is user friendly and participants were given their unique and secure username and password to log in to

complete questionnaires. A programme was set up to notify users when they were needed to complete the PROM. If patients chose to have paper based questionnaires, these were sent at scheduled times after confirming the patient's status with local research nurses or general practitioners, to exclude those who had progressed or died. Patients were reminded by phone to complete and return the data on time.

In SOCQER-2, most of the patients chose the paper based method and only a few wished to complete web based questionnaire. Most of these patients switched to paper based questionnaires during the course of study. Once PROMs were received at UOB, the data were checked for quality; any missing questions were discussed with participants directly and then transferred to the REDcap system for storage.

**Patient reported outcome data tools:** There is consensus that PROs should be context specific, population specific and aimed towards objectives of treatment in ovarian cancer clinical trials and should also include progression free survival as an endpoint where PROs are primary endpoint (Joly et al., 2017). EORTC provides QLQ-C30 and OV28 which includes questions for general cancer patients and an ovarian specific module. Other forms of QoL assessment tools have also been used in the past, such as Functional Assessment of Cancer Therapy – General (FACT-G) and Functional Assessment of Cancer Therapy – Ovarian (FACT-O) (Cella et al., 1993, Basen-Engquist et al., 2001). In spite of these, other aspects of QoL, such as effect of stoma, urological surgery, psychological stress and mental health remain unanswered. The National Cancer Institute has discussed the recommended core sets for various QoL domains and symptoms for ovarian cancer and also for other

cancer trials, which should be included in PROs in all ovarian cancer trials and observational studies (Donovan et al., 2014, Reeve et al., 2014). In our study, we decided to use EORTC QLQ-C30, OV28, subsets of CR29 & PR25, Hospital Anxiety and Depression Score (HADS), Fear of progression (FOP) and EQ-5D-5L. As the majority of patients in Kolkata (India) may not understand questionnaires in English, SK organised the translation of the required questionnaires (EORTC QLQ OV28, CR29 and PR25) in Bengali (the local language in the region) with collaboration of EORTC QLQ Translation Group and native speakers of Bengali language as per EORTC guidelines. SK's efforts were appreciated by EORTC group and a certificate of acknowledgement was presented (Appendix SQR6, page 152).

In order to include all possible domains of QoL and symptoms of ovarian cancer and treatment related impairments as recommended for QoL data collection in clinical trials, the following QoL assessment tools were utilised as a part of PROMs in SOCQER-2 study at pre surgery, 6 weeks, 6 months, 12 months, 18 months and 24 months post-surgery (Figure 2).

1. ***European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30), version 3:*** The EORTC QLQ-C30 (Aaronson et al., 1993) is a well-established, psychometrically sound, internationally used cancer-specific measure of health-related quality of life. It comprises 30 items including five functioning scales, three symptom scales, six single items and one global scale of quality of life core questionnaire. Items (excepting the two global quality of life items) are rated on a scale of 1 (not at all) to 4 (very much) with respect to the past week or month. Higher scores on functioning scales are indicative of high/healthy

functioning, whereas higher scores on symptom scales are indicative of a higher level of symptomatology /problems (Appendix SQR7, page 153).

2. ***European Organisation for Research and Treatment of Cancer Ovarian Cancer module (EORTC QLQ- OV28):*** This 28-item ovarian cancer specific module assesses abdominal/gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side-effects, hormonal/menopausal symptoms, body image, attitude to disease/treatment and sexual functioning. Scoring is as described for the QLQ-C30 (Appendix SQR8, page 157).
3. ***European Organisation for Research and Treatment of Cancer Colorectal Cancer module (EORTC QLQ- CR29), items 49-55 only:*** This 29 item module comprises 4 scales and 19 single items and was developed initially for use with colorectal cancer patients (Whistance et al., 2009). A subset of six or seven (dependent upon the presence of a stoma bag) items were administered for SOCQER-2 including: the Frequency of Bowel Movements subscale (2 items) and four single items relating to flatulence, stool leakage, soreness of the skin, and embarrassment due to bowel movements plus an additional single item for stoma care management for those with a stoma bag only. Scoring is as described for the QLQ-C30.
4. ***European Organisation for Research and Treatment of Cancer Prostate Cancer module (EORTC QLQ- PR25), items 31-39 only:*** The QLQ- PR25 was developed for administration in prostate cancer studies. It has 25 items forming two functioning scales, three symptom scales and one single item (van Andel et al., 2008). The Urinary Symptoms subscale (7 items) and the

single item on use of an incontinence aid were included in SOCQER-2. Scoring is as described for the QLQ-C30.

5. ***EQ-5D-5L:*** The EQ-5D-5L (Herdman et al., 2011) is a more recent development of the well-established, internationally used generic measure of health status developed originally by the EuroQol Group in 1990. The EQ-5D-5L still consists of a descriptive system with the same 5 dimensions as the EQ-5D-3L (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). However, each dimension now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. These are followed by the EQ Visual Analogue scale (EQ-VAS) on which health state today is rated from 0 (worst imaginable health state) to 100 (best imaginable health state). The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state.
6. ***Hospital Anxiety and Depression Scale (HADS):*** The HADS was developed for screening physically ill patients for clinically significant emotional distress (Zigmond and Snaith, 1983). It consists of 14 questions organised in two scales: Anxiety and Depression with a score range for each scale from 0 - 21 and a higher score indicating a higher level of psychological distress. The two scales may be combined to form an overall score of psychological distress (range 0 - 42).
7. ***Fear of Progression (FOP) short-form questionnaire:*** The FOP-short form is a 12 item questionnaire derived from the original version (Herschbach et al., 2005). The 12 items, rated on a five-point scale ranging from never to

very often, form a unidimensional scale with higher scores indicating greater levels of fear (Mehnert et al., 2006).

In this thesis, QoL outcomes will be reported using EORTC QLQ-C30 and EORTC QLQ-OV28 for different types of the extent of surgery. Further exploration of QoL outcomes as per timing of surgery, presence of upper abdominal disease at surgery and residual disease status after surgery will be reported as a summary. The detailed discussion is beyond the scope of this thesis.

**Data management and quality assurance:** The data received from each centre was assessed for its quality and relevance by 2 experienced researchers (SK, JL) and discussed with project supervisors (SS, CC) if any inconsistencies were noted. Any queries related to clinical data were discussed with the research nurse or principal investigator at data providing centres and all possible efforts were made for the completeness and quality. The research nurse from the participating site was contacted prior to sending the questionnaire to the patients. Data related to PRO were discussed directly with the patients over telephone if there were any unusual or missing data, as soon as they were received. The reported data's quality and completeness were discussed at monthly supervision meetings (SK, JL, SS, and CC). All paper based data were transferred to REDcap software at the University of Birmingham (SK, JL). Data was downloaded for analysis to SPSS v22 at regular intervals and a copy for backup was saved on a secure University of Birmingham server.

**Statistical analysis:** The primary outcome measures were QoL measured by the EORTC QLQ-C30, QLQ-OV28 and progression free survival. Secondary outcomes

were survival, other PROMs measures, and post-operative morbidities. Therefore, participants in this study were classified into 3 groups: women having surgery with low SCS (score 1 to 3), intermediate SCS (score 4 to 7) and high SCS (score 8 and above). Differences between the groups were analysed at baseline using descriptive statistics appropriate for the level of measurement and sample distribution. Outcome variables (composite quality of life and survival) for each of the groups were also summarised using means, median or percentages as appropriate. As this is an observational study, residual confounding cannot be ruled out, and reporting of results will acknowledge this. Nonparametric tests (Kruskal Wallis or Mann Whitney U test) were used to compare in between group differences at any given point. For the QoL outcomes, variables were analysed using general linear repeated measures with statistical tests for within and in between group differences in a complete case analysis using data from 6 weeks to 12 months post-surgery. After 12 months there would be fewer cases due to the increasing rate of progression. So, the repeated measures model would only include data for up to 12 months. Test for sphericity and fit was carried out. Post hoc comparisons were made using Bonferroni's adjusted p-value. Data imputation techniques were not used where data on quality of life or other outcome variables were missing. No adjustment to the alpha value to allow for multiple testing of subscales was made as the acknowledged purpose of analysis of subscale outcomes would be hypothesis generating. All statistical analysis was conducted in SPSS v24.

Participants' data were censored for survival outcomes at the time of progression of disease or death or at the end of 2 years of follow-up. Differences in patient

population and treatments were explored to confirm whether centres had different treatment policies and whether patient characteristics varied by centres.

Descriptive analyses included:

- Characteristics of patients undergoing “extensive” or “standard” surgery.
- Identification of variation in patient selection and types of surgical intervention at different centres.
- Association of specific components of ovarian cancer surgery (timing, complexity, disease burden and residual disease status) with different aspects of quality of life.
- Association of surgical variables and survival outcomes (PFS and OS).

### Scoring of Patient reported outcome data

The EORTC QoL data were analysed as per EORTC QLQ-C30 and other supplementary modules manual (Fayers PM, 2001). QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning; a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems. The principle for scoring these scales is the same in all cases (Appendix SQR9, page 159). A small change in QoL is reflected by a change in 5 – 10 points, moderate change by 10 –

20 points and large change by more than 20 points difference in either direction (Osoba et al., 1998). In this thesis, we considered a 10 points change in QoL score as a clinically significant change as was also considered in EORTC55971 (Greimel et al., 2013).

### Survival analysis: Methods

Kaplan-Meier analysis was used for overall survival and progression free survival. Progression-free survival was calculated from the date of diagnosis to the date of the first indication of disease progression (either by clinical assessment, rise in CA125 or radiological assessment) or death, whichever occurred first. Overall survival was calculated from the date of diagnosis to the date of death. The date of diagnosis for NACT patients was taken as the date of first biopsy result prior to chemotherapy. The date of surgery was taken as diagnosis date for those patients who had primary debulking surgery. Patients were censored at two years of follow-up or at date lost to follow-up. Groups were compared using a log-rank test. Cox proportional hazard models of progression free and overall survival were produced with adjusted hazard ratios using a forward stepwise procedure including the variables surgical complexity score (low, intermediate, high), baseline treatment plan (NACT or PDS), pre-surgical albumin level of <35g/l or >=35g/l, aged >=65 or <65, Age-Adjusted Charlson score of <2 or >=2, maximum level of disease (pelvic disease only, pelvic and mid abdominal disease or upper abdominal and other diseases), and pre-operative Peritoneal Carcinomatosis Index (<5, between 6 and 14, or >=15) and UK or India patient with likelihood ratio tests of contribution to model determining entry and exit to models at each step. Survival analysis was carried out using SPSS 24.

## Sample size calculation:

The SOCQER2 protocol included sample size calculations based on the minimum requirements to meet the objectives of NICE as the funder of the study but aimed to recruit as large a sample as possible in the recruitment period to increase study power. In sample size for repeated measures, it is common practice to pick a single time point and calculate sample based on a single difference in group means, inflating sample size for dropout to give a conservative estimate. If it is assumed that the ratio of group sizes for very extensive v standard surgery is 2:1, with alpha of .05 and power of 80% and that a 13 point difference would be of clinical importance (assuming QLQ-30 of those undergoing very extensive surgery is 66 (SD24 (as per EORTC scoring manual)), a sample size of 123 (standard=41 and extensive=82) would be required, with an additional allowance for dropout (calculations made in Stata 13.1). This would also be adequate to demonstrate subscale differences: there would be no adjustment to the alpha value to allow for multiple testing of subscales as the acknowledged purpose of analysis of subscale outcomes would be hypothesis generating.

# Results:

## Recruitment:

A total of 293 patients were recruited into SOCQER-2 study from 12 cancer centres in the UK (n=235) and one centre in India (n=58) over a period of 12 months. After completion of their surgical intervention and final histopathology, 247 (84%) patients were eligible to remain under SOCQER-2 study. Forty-six (16%) patients were excluded from the study as they did not satisfy the inclusion criteria (Table 5).

**Table 5: Reasons for exclusion of subjects recruited in SOCQER-2 study**

| Reasons for exclusion | Frequency | Percentage of total recruited |
|---|---|---|
| **Inoperable (open/close)** | 13 | 4.4 |
| **Lower stage (Stage 1 / 2)** | 15 | 5.1 |
| **Benign/Borderline** | 4 | 1.4 |
| **Patient did not have Surgery** | 7 | 2.4 |
| **Not ovarian cancer** | 5 | 1.7 |
| **Withdrew consent** | 2 | 0.7 |
| **Total** | 46 | 15.7 |

# Completion rate of PRO data:

**Table 6: Data completion rate and loss to follow-up**

| Time points | PRO data completed | PRO data expected (n=247) | Percentage of PRO data completed | Reasons for change in eligible participants at each time point |
|---|---|---|---|---|
| **Baseline** | 221 | 242 | 91.3% | 5 withdrew consent for PROMs data collection |
| **6 weeks** | 217 | 238 | 91.2% | 1 progressed / 3 deaths |
| **6 months** | 205 | 229 | 89.5% | 9 progressed |
| **12 months** | 142 | 173 | 82.1% | 56 progressed |
| **18 months** | 103 | 108 | 95.4% | 65 progressed |
| **24 months** | 61 | 85 | 71.2% | 23 progressed |

Out of 247 patients recruited into the study 221 (89.5%) patients completed their pre-surgical baseline PRO data. 21 patients missed completing the questionnaire while 5 patients withdrew their consent prior to returning any PRO data. Details of the flow diagram and proportions of completed PROMs are provided in Table 6 and Appendix SQR10, page 160. Figure 9 demonstrates the flow chart of patients recruited in the study and their loss to follow up rate according to surgical complexity score (SCS), primarily to identify if there are important differences in loss to follow-up rate that may be plausibly explained by poorly patients unable to return PRO data.

Non-completion of PROMs was more prominent in eligible participants with low SCS group. While more than 80% of patients have consistently returned PRO data in intermediate and high SCS group, the return rate of PRO data was fallen to 70% at 12 months to 18 months and 46% at 24 months in low SCS group without any obvious reasons.

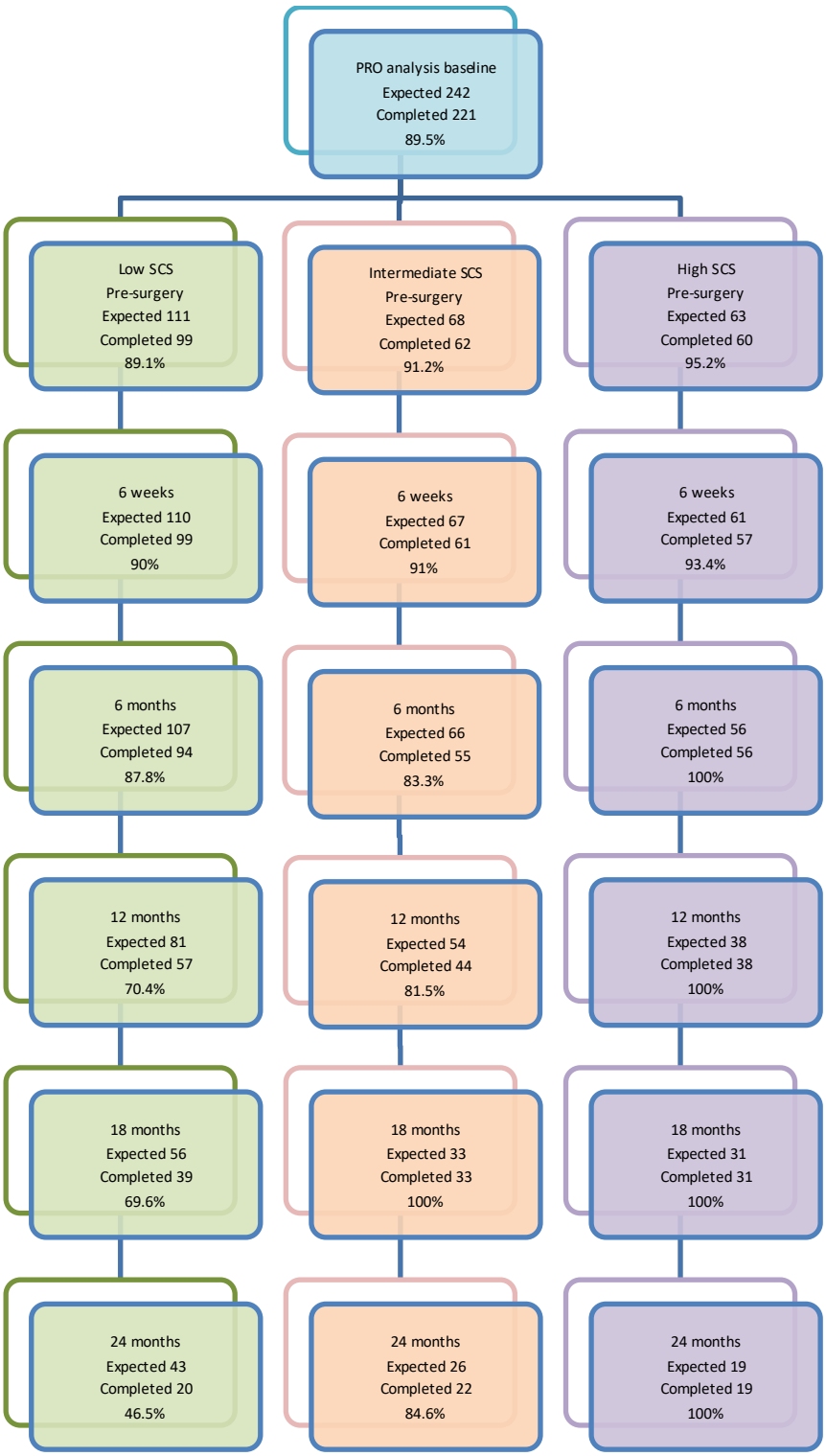



**Figure 9: PRO completion rate by surgical complexity scores**

## Overall characteristics of patients in SOCQER-2 study:

**Pre-operative:** Median age of the patients in the study was 63 (IQR 16, range 18 – 85) years. For UK and Indian patients, the median age was 65 years and 55 years respectively (p=0.001). 89% patients had an ECOG performance status of 0 – 1, 64% had ACCI of 2 or less and 78% patients had normal pre-operative albumin levels (≥35g/L). 70% patients received NACT followed by debulking surgery, while 30% had upfront primary debulking surgery followed by chemotherapy (Table 7).

**Intra-operative:** Pre-operative median PCI was 11. However, 1/3$^{rd}$ of the patients in the study had PCI of 6 or lower. In our cohort, 61% of patients had upper abdominal disease.

Low SCS (score 1 – 3) were found in 46% of patients, 28% had intermediate SCS (score 4 – 7) and 26% patients had high SCS (score 8 and more). In our cohort, "no residual disease" status was achieved for 62% patients, while residual disease status of "less than 1 cm" was achieved in 27% of patients. Sub-optimal outcome (residual disease status of more than 1 cm) was recorded for 11% of patients. Large bowel resections were performed in 66 (27%) patients, and 22 (33%) of these had primary end to end anastomosis. Liver mobilisation and diaphragmatic peritonectomy / resections were performed in 53 (22%) patients and 21 (9%) patients had splenectomy. Details of these procedures are provided in Table 8. Significant intra-operative complications were reported for 20 (8%) patients; details of these complications are provided in Table 8 and are discussed in the later section of the thesis.

**Post-operative:** Clavien-Dindo grade 3, 4 and 5 morbidities were reported for 35 (14%) patients, of which 3 (1.2%) patients died post-operatively by 6 weeks from complications of surgery. The median length of in-patient hospital stay was 6 (IQR 4) days and median surgery to chemotherapy interval was 34 (IQR 16) days. 90% patients had high grade serous cancer and 91% patients had either FIGO stage 3C or 4 (Table 8).

**Table 7: Preoperative and intra-operative characteristics of included patients in SOCQER-2 (n=247)**

| Patient characteristics | Variables | Number | Percentage (%) |
|---|---|---|---|
| Age, years | Median (IQR) | 63 (16) | |
| | Up to 65 years | 143 | 58 |
| | More than 65 years | 104 | 42 |
| | | | |
| Eastern Co-operative Oncology Group Performance status | 0 | 107 | 43 |
| | 1 | 113 | 46 |
| | 2, 3 & 4 | 27 | 11 |
| | | | |
| Age adjusted Charlson Comorbidity Index | 0 | 39 | 16 |
| | 1 | 51 | 21 |
| | 2 | 67 | 27 |
| | 3 | 58 | 24 |
| | 4 | 22 | 9 |
| | 5 – 6 | 10 | 4 |
| | | | |
| Body mass index | Mean (SD) | 27 (5.4) | |
| | Up to 25 | 110 | 45 |
| | More than 25 | 134 | 55 |
| | | | |
| Pre-surgery Haemoglobin g/L (WHO, 2011) | Up to 109 g/L | 102 | 41 |
| | 110 g/L or above | 145 | 59 |
| | | | |
| Pre-surgery albumin level | Mean (SD) | 38 (6.1) | |
| | Up to 35 g/L | 53 | 22 |
| | More than 35 g/L | 194 | 78 |
| | | | |
| Timing of surgery | Primary debulking surgery | 75 | 30 |
| | Surgery after NACT | 172 | 70 |
| | | | |
| Peritoneal carcinomatosis index (PCI) | Median (IQR) | 11 (13) | |
| | Up to 6 | 85 | 34 |
| | 7 to 12 | 56 | 23 |
| | More than 12 | 106 | 43 |
| | | | |
| Level / distribution of disease | Level 1 (None / pelvis only) | 27 | 11 |
| | Level 2 (Pelvis and mid-abdomen only) | 69 | 28 |
| | Level 3 (Pelvis, mid-abdomen and upper abdomen) | 151 | 61 |
| | | | |
| Aletti's surgical complexity score (SCS) | Low ( SCS up to 3) | 113 | 46 |
| | Intermediate (SCS 4 – 7) | 70 | 28 |
| | High (SCS ≥ 8) | 64 | 26 |

**Table 8: Post-operative characteristics of all patients in SOCQER-2**

| Patient characteristics | Variables | Number | Percentage (%) |
|---|---|---|---|
| Outcome of surgery | No visible residual disease (CC-0) | 153 | 62 |
| | Less than 1 cm residual disease (CC-1) | 67 | 27 |
| | 1 cm or more residual disease (CC-2) | 27 | 11 |
| | | | |
| Final histopathology | High grade serous carcinoma | 222 | 90 |
| | Low grade serous carcinoma | 9 | 3.6 |
| | Clear cell carcinoma | 11 | 4.4 |
| | Endometrioid | 4 | 1.6 |
| | Others | 5 | 2 |
| | | | |
| Types of chemotherapy | Carboplatin +/- Taxol | 230 | 93 |
| | Carboplatin, Taxol + Bevacizumab | 43 | 17 |
| | Other | 12 | 5 |
| | No post-op chemotherapy | 5 | 2 |
| | | | |
| Final FIGO (International Federation of Obstetricians and Gynaecologists) stage | 3A | 5 | 2 |
| | 3B | 17 | 7 |
| | 3C | 135 | 55 |
| | 4 | 86 | 35 |
| | Not reported | 4 | 1 |
| | | | |
| Length of hospital admission | Median (IQR) | 6 (4) | |
| | | | |
| Surgery to chemotherapy interval | Median (IQR) | 34 (16) | |
| | | | |
| Types of surgical resections | TAH, BSO | 240 | 97.2 |
| | Omentectomy | 239 | 96.8 |
| | Pelvic peritonectomy | 133 | 53.8 |
| | Parietal peritonectomy | 94 | 38.1 |
| | Pelvic lymphadenectomy | 69 | 27.9 |
| | Para-aortic lymphadenectomy | 69 | 27.9 |
| | Small bowel resection | 19 | 7.7 |
| | Large bowel resection with end colostomy | 38 | 15.4 |
| | Large bowel resection with primary end to end anastomosis | 22 | 8.9 |
| | Liver mobilisation / resection | 46 | 18.6 |
| | Diaphragmatic peritonectomy / resection | 53 | 21.5 |
| | Splenectomy | 21 | 8.5 |
| | Resection of disease from lesser sac | 12 | 4.9 |
| | Cholecystectomy | 4 | 1.6 |
| | More than one bowel resections | 6 | 2.4 |
| | | | |
| Types of intraoperative complications | None | 227 | 92 |
| | Haemorrhage | 1 | 0.4 |
| | Urinary tract injury | 5 | 2 |
| | GI injury | 5 | 2 |
| | Vascular injury | 5 | 2 |
| | Anaesthetic complications | 4 | 1.6 |
| | | | |
| Post-operative morbidities (Clavien-Dindo classification) | None, Grade 1 or Grade 2 | 212 | 86 |
| | Grade 3 | 24 | 10 |
| | Grade 4 | 8 | 3 |
| | Grade 5 | 3 | 1.2 |

**Characteristic of patients by surgical complexity score groups:**

Table 9 shows the patient's characteristics by SCS. 113 (46%) patients had low complexity surgery, 70 (28%) patients had intermediate complexity surgery and 64 (26%) had high complexity surgery. Pre-operatively, statistically significant differences were present in age, ACCI, and ECOG performance status of patients in these groups. Intermediate and high SCS group had more patients younger than 65 years, with better performance status and less co-morbidity. 172 (70%) patients had NACT followed by surgery and 75 (30%) underwent PDS. Among the NACT group, 103 (60%) patients had low SCS, 44 (25%) had intermediate SCS and 25 (15%) had high complexity surgery. Among PDS group, only 10 (13%) patients had low SCS, 26 (35%) had intermediate SCS and 39 (52%) had high SCS (p=0.001).

151 (61%) patients had upper abdominal disease. 48 (42.5%) patients of these underwent low complexity surgery following which these patients had residual disease after surgery. 2 additional patients in the low SCS group, who did not have upper abdominal disease also had residual disease post-surgery. Therefore, 50/113 (44%) patients who had low SCS surgery, had residual disease, of which 29 (26%) patients were estimated to have less than 1 cm residual disease and 21 (19%) patients had more than 1 cm residual disease. Overall, 62% patients achieved no residual disease status after surgery and 27% had optimal debulking. 27 (11%) patients had residual disease more than 1 cm size (sub-optimal debulking), of which 26 were due to residual disease present in the upper abdomen (Table 12).

The median length of hospital admission was similar in low (5 days) and intermediate (6 days) complexity surgery group but higher (9 days) in the high SCS group of patients (p=0.001). Similarly, median interval between surgery and post-

operative chemotherapy was 31 days in low and intermediate SCS group but for high SCS group it was 39 days (p=0.005).

Due to geographical variation between UK and Indian patients, a comparative analysis was performed. Statistically significant difference was observed in age, pre-operative albumin level, ACCI, PCI and SCS between UK patients and Indian patients. This difference is reflected by the utilization of neoadjuvant chemotherapy by UK institutions (75%) and the participating centre in India (48%), leading to lower median PCI in UK patients compared to Indian patients. The differences in baseline characteristics of UK and Indian patients are provided in Table 10.

**Table 9: Baseline characteristics of patients as per Aletti's surgical complexity scores**

| Patient characteristics | Low SCS N=113 | | Intermediate SCS N=70 | | High SCS N=64 | | P value |
|---|---|---|---|---|---|---|---|
| | Number | % | Number | % | Number | % | |
| Age, years | | | | | | | |
| **Up to 65 years** | 51 | 45.1 | 44 | 62.9 | 48 | 75 | 0.001 |
| **More than 65 years** | 62 | 54.9 | 26 | 37.1 | 16 | 25 | |
| Eastern Co-operative Oncology Group Performance status | | | | | | | |
| **0** | 53 | 46.9 | 35 | 50 | 19 | 29.7 | 0.046 |
| **1** | 52 | 46 | 25 | 35.7 | 36 | 56.3 | |
| **2, 3 & 4** | 8 | 7.1 | 10 | 14.3 | 9 | 14.1 | |
| Age adjusted Charlson Comorbidity Index | | | | | | | |
| **0 – 2** | 62 | 54.9 | 49 | 70 | 46 | 71.9 | 0.033 |
| **3 and higher** | 51 | 45.1 | 21 | 30 | 18 | 28.1 | |
| Body mass index | | | | | | | |
| **Up to 25** | 42 | 37.2 | 37 | 52.9 | 31 | 48.4 | 0.096 |
| **More than 25** | 69 | 61.1 | 32 | 45.7 | 33 | 51.6 | |
| Timing of surgery | | | | | | | |
| **PDS** | 10 | 8.8 | 26 | 37.1 | 39 | 60.9 | 0.001 |
| **NACT** | 103 | 91.2 | 44 | 62.9 | 25 | 39.1 | |
| Pre-surgery Haemoglobin (WHO, 2011) | | | | | | | |
| **Up to 109 g/L** | 49 | 43.4 | 28 | 40.0 | 25 | 39.1 | 0.827 |
| **110 g/L or above** | 64 | 56.6 | 42 | 60.0 | 39 | 60.9 | |
| Pre-surgery albumin level | | | | | | | |
| **Up to 35 g/L** | 22 | 19.5 | 14 | 20 | 17 | 26.6 | 0.511 |
| **More than 35 g/L** | 91 | 80.5 | 56 | 80 | 47 | 73.4 | |
| Peritoneal carcinomatosis index | | | | | | | |
| **Up to 6** | 65 | 57.5 | 18 | 25.7 | 2 | 3.1 | 0.001 |
| **7 to 12** | 21 | 18.6 | 29 | 41.4 | 6 | 9.4 | |
| **More than 12** | 27 | 23.9 | 23 | 32.9 | 56 | 87.5 | |
| Level / distribution of disease | | | | | | | |
| **Level 1 (None / pelvis only)** | 20 | 17.7 | 7 | 10 | 0 | 0 | 0.001 |
| **Level 2 (Pelvis and mid-abdomen)** | 45 | 39.8 | 19 | 27.1 | 5 | 7.8 | |
| **Level 3 (Pelvis, mid-abdomen and upper abdomen)** | 48 | 42.5 | 44 | 62.9 | 59 | 92.2 | |
| Presence of upper abdominal disease | | | | | | | |
| **Not present** | 65 | 57.5 | 26 | 37.1 | 5 | 7.8 | 0.001 |
| **Present** | 48 | 42.5 | 44 | 62.9 | 59 | 92.2 | |
| Outcome of surgery | | | | | | | |
| **No visible residual disease (n=153, 62%)** | 63 | 55.8 | 50 | 71.4 | 40 | 62.5 | 0.007 |
| **< 1 cm residual disease (n=67, 27%)** | 29 | 25.7 | 17 | 24.3 | 21 | 32.8 | |
| **1 cm or more** | 21 | 18.6 | 3 | 4.3 | 3 | 4.7 | |

| Patient characteristics | Low SCS N=113 | | Intermediate SCS N=70 | | High SCS N=64 | | P value |
|---|---|---|---|---|---|---|---|
| **residual disease (n=27, 11%)** | | | | | | | |
| | | | | | | | |
| Final FIGO (International Federation of Obstetricians and Gynaecologists) stage | | | | | | | |
| **3A/3B (n=22)** | 11 | 9.7 | 9 | 12.9 | 2 | 3.1 | |
| **3C (n=135)** | 68 | 60.2 | 34 | 48.6 | 33 | 51.6 | |
| **4 (n=86)** | 31 | 27.4 | 26 | 37.1 | 29 | 45.3 | |
| **Not available (n=4)** | 3 | 2.7 | 1 | 1.4 | 0 | 0 | |
| | | | | | | | |
| Details of post-operative chemotherapy | | | | | | | |
| **Carboplatin+/- Taxol** | 106 | 94 | 62 | 89 | 62 | 97 | |
| **C,T+Bevacizumab** | 20 | 18 | 15 | 21 | 8 | 13 | |
| **Other** | 5 | 4 | 5 | 7 | 2 | 3 | |
| **No chemotherapy** | 2 | 2 | 3 | 4 | 0 | 0 | |
| | | | | | | | |
| United Kingdom / India patient | | | | | | | |
| **UK (n=195)** | 108 | 95.6 | 53 | 75.7 | 34 | 53.1 | 0.001 |
| **India (n=52)** | 5 | 4.4 | 17 | 24.3 | 30 | 46.9 | |
| | | | | | | | |
| Pre-surgery Global QoL score, Score (SD) | 65.1 (21.7) | | 59.8 (19.9) | | 58.1 (22.2) | | 0.094 |
| | | | | | | | |
| | Median, days | IQR | Median, days | IQR | Median, days | IQR | |
| Length of hospital admission (days, median, IQR) | 5 | 3 | 6 | 3 | 9 | 8 | 0.001 |
| | | | | | | | |
| Surgery to chemotherapy interval (days, median, IQR) | 31 | 16 | 31 | 13 | 39 | 20 | 0.005 |
| | | | | | | | |

**Table 10: Differences in baseline characteristics of UK and Indian patients**

| | p value | Mean Difference | 95% Confidence Interval of the Difference | |
|---|---|---|---|---|
| | | | Lower | Upper |
| **Age** | 0.001 | 10.2 | 6.8 | 13.5 |
| **Body mass index** | 0.841 | 0.2 | -1.5 | 1.8 |
| **Pre-operative albumin** | 0.014 | -2.3 | -4.2 | -0.5 |
| **Age adjusted Charlson comorbidity score** | 0.001 | 0.8 | 0.4 | 1.2 |
| **Peritoneal Carcinomatosis Index** | 0.001 | -6.7 | -9.2 | -4.1 |
| **Aletti's surgical complexity score** | 0.001 | -5.9 | -7.2 | -4.6 |
| **Length of inpatient admission** | 0.061 | -2.1 | -4.3 | 0.1 |
| **Surgery to chemotherapy interval** | 0.104 | 3.8 | -0.8 | 8.5 |

### Relationship observed for PCI and extent of surgery:

On analysis of PCI by SCS (Figure 10), two distinct types of patients were observed: first group who underwent low and intermediate complexity surgery and a second group who had high complexity surgery. With the exception of a few patients, PCI was very similar in low complexity surgery and intermediate complexity surgery group, but these patients had different types of surgery. As a result, sub-optimal outcomes for residual disease were more prominent in low SCS group (Table 13, Figure 11). Exploring this further, I analysed the level of disease with SCS type received and residual disease status to see if there is a particular group of patients at higher risk of sub-optimal outcomes. Table 11, 12 and 13 segregates these patients based on the level of disease and show that patients having upper abdominal disease burden but undergoing low complexity surgery are at risk of sub-optimal outcome for residual disease. This association could possibly be explained by patient's baseline characteristics such as advanced age, performance status, comorbidities or it could be related to variations in practice by different institutions or surgeons.

PCI was also differently distributed between women undergoing PDS or NACT. A total of 30% patients had PDS and 70% patients had NACT followed by surgery. The peritoneal carcinomatosis variations in these two categories (Figure 12) demonstrate that even though the disease burden in the NACT group is lower than that of the PDS group, there is a significant overlap in on both groups. Utilization of NACT to reduce the disease load is partially effective, as in our cohort, 94 (54%) patients in NACT group were found to have upper abdominal disease.

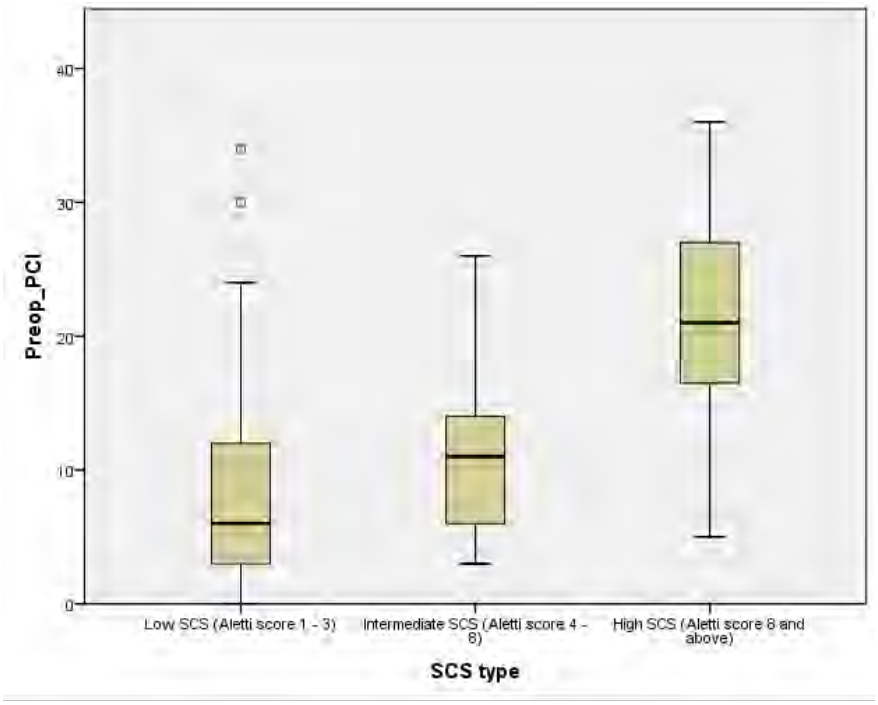



**Figure 10: Distribution of PCI by SCS type**

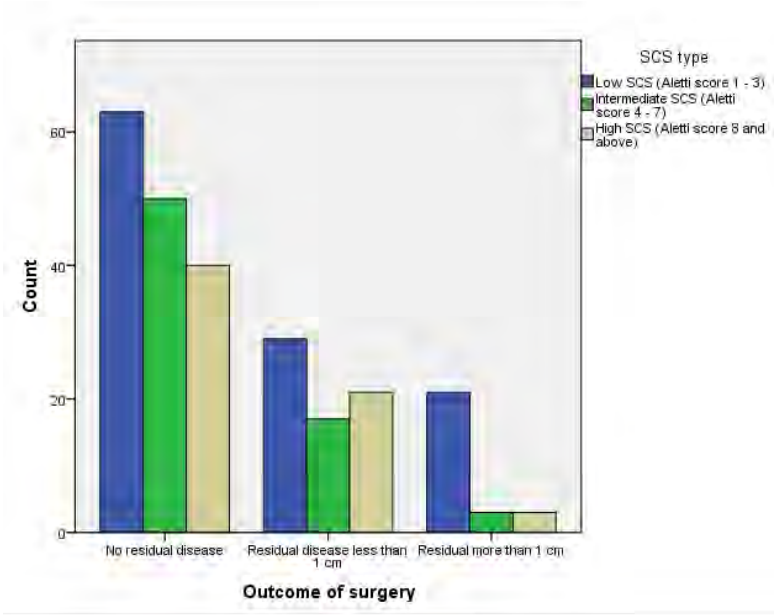



**Figure 11: Residual disease status by SCS type**

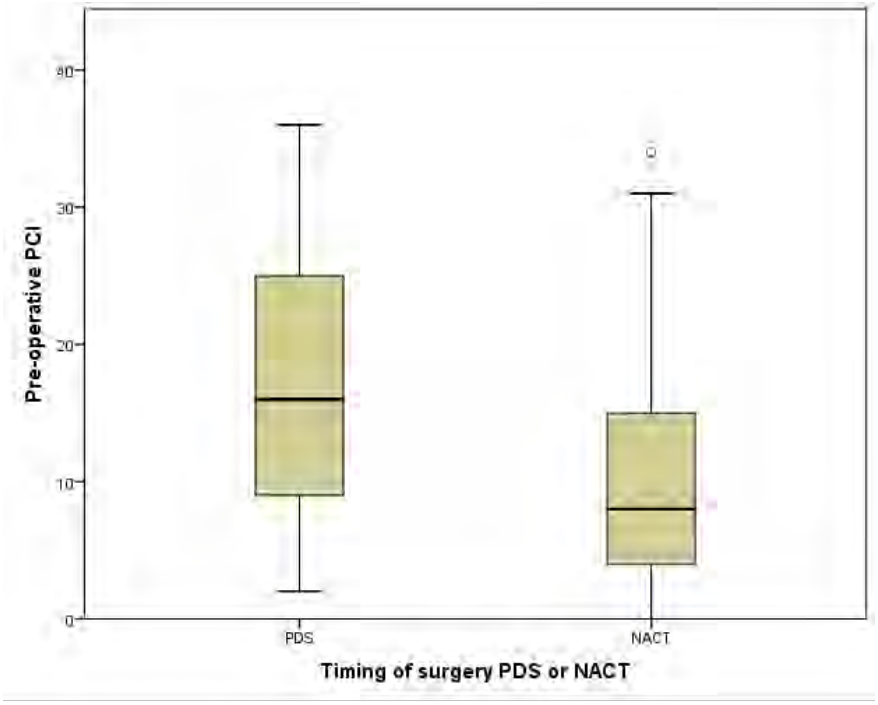



**Figure 12: Distribution of PCI in PDS and NACT group**

**Table 11: Relationship observed between maximum level of disease and SCS**

| | | SCS type | | | Total |
|---|---|---|---|---|---|
| | | Low SCS (Aletti score 1 - 3) | Intermediate SCS (Aletti score 4 - 7) | High SCS (Aletti score 8 and above) | |
| Max Level | Pelvic disease only | 20 | 7 | 0 | 27 |
| | Pelvic and mid abdominal disease | 45 | 19 | 5 | 69 |
| | Upper abdominal and other disease | 48 | 44 | 59 | 151 |
| Total | | 113 | 70 | 64 | 247 |

**Table 12: Relationship observed for maximum level of disease and outcome of surgery**

| | | Outcome of surgery | | | Total |
|---|---|---|---|---|---|
| | | No residual disease | Residual disease less than 1 cm | Residual more than 1 cm | |
| Max Level | Pelvic disease only | 26 | 1 | 0 | 27 |
| | Pelvic and mid abdominal disease | 61 | 7 | 1 | 69 |
| | Upper abdominal and other disease | 66 | 59 | 26 | 151 |
| Total | | 153 | 67 | 27 | 247 |

**Table 13: Relationship between SCS and residual disease status**

| | | Outcome of surgery | | | Total |
|---|---|---|---|---|---|
| | | No residual disease | Residual disease less than 1 cm | Residual more than 1 cm | |
| SCS type | Low SCS (Aletti score 1 - 3) | 63 | 29 | 21 | 113 |
| | Intermediate SCS (Aletti score 4 - 7) | 50 | 17 | 3 | 70 |
| | High SCS (Aletti score 8 and above) | 40 | 21 | 3 | 64 |
| Total | | 153 | 67 | 27 | 247 |

**Time utilization in debulking surgery:** Time utilization for debulking surgery depends on the disease load, complexity of surgeries and to some extent it is operator dependent as well. In our cohort, it corresponded directly to the SCS. In higher complexity surgeries, it usually took more than 6 hours per patient (Figure 13). In 3 patients, it was reported to be within 3 hours, and in 8 patients, it was between 3 to 4 hours, and among these patients 9 cases were reported to have no residual disease status and 2 patients had optimal outcome (residual disease less than 1 cm). Most of the patients where residual disease status was more than 1 cm, had less time consuming surgery and most of these patients had upper abdominal disease, it is possible that an attempt to resect these upper abdominal diseases was not considered appropriate by the operating team.

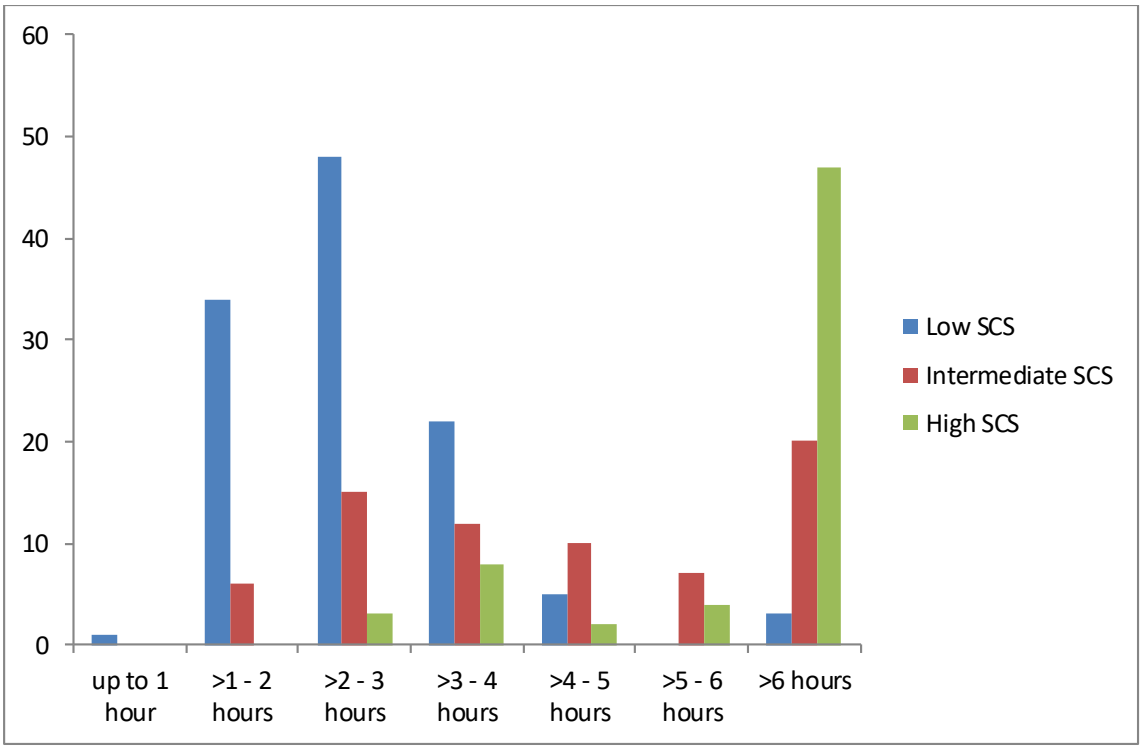



**Figure 13: Time utilized during surgery: SCS types**

## Overall reported morbidity for patients in SOCQER-2

As there are clear variations in UK and Indian cohorts due to their baseline characteristics (Table 10), disease load and types of surgical interventions, they are analysed separately and collectively. The analysis of post-operative morbidity and mortality is performed based on extent of surgical complexity and also by timing of surgery.

### Intra-operative complications and extent of surgery:

Overall, major intra-operative complications were reported for 20 (8.1%) patients undergoing debulking surgery in the cohort. They included major haemorrhage, anaesthetic complications or injury to the urinary tract, bowels or major blood vessels and reported by surgeons directly. The details of these complications are provided in Table 14 and stratified by UK vs India, surgical complexity and timing of surgery (PDS vs NACT). Total reported complications were higher in the PDS group and in higher complexity surgeries, however, there was no statistical difference in their occurrence either by SCS type (p=0.875) or timing of surgery (p=0.231).

### Post-operative complications and extent of surgery:

Overall, 30% patients reported to have minor or major post-operative complications as per Clavien-Dindo grading of post-operative morbidity (Table 15). The incidences of overall morbidities is higher for Kolkata vs UK (56% vs 23%, p<0.001), PDS vs NACT (44% vs 23%, p=0.017) and SCS type (low SCS 20% vs Intermediate SCS 26% vs High SCS 52%, p<0.001). However, these morbidities included grade 2 morbidities, such as blood transfusion, antibiotics for pyrexia, conservatively managed wound infections etc. that may not be considered significant by many surgeons. After excluding grade 2 morbidities, overall incidence of significant post-operative morbidity (Grade 3, 4 & 5) was 14.2% (UK – 11.2% and India – 25%).

Higher rates of complications of grade 3 and above were observed for PDS (24%) against NACT (10%). Surgery with high SCS had 25% morbidity, while surgeries with intermediate SCS and low SCS were reported to have 13% and 9% morbidities (Table 16). Three (1.2%) patients died due during post-operative period, one of them had low complexity surgery and the remaining 2 patients had intermediate complexity surgery. A limitation of our study is that any complications persisting or occurring after 6 – 8 weeks are unlikely to have been reported. However, such complications would have been captured through its impact on PROMs. Table 17 describes actual events as reported by participating centres.

Analysis of post-operative deaths within 6 weeks of surgery:

Case 1: 46 year women, underwent PDS of SCS score 5 (diaphragmatic peritonectomy), suffered from disseminated intravascular coagulation, multi-organ failure. Death was reported 2 days after discharge from the intensive care unit on $20^{th}$ day.

Case 2: 76 year old women with a history of diabetes and previous cerebrovascular disease, underwent NACT followed by debulking surgery. The patient sustained rectal perforation during surgery. The patient received low complexity surgery and had optimal cytoreduction. Sudden death in the hospital was reported on $16^{th}$ day post-surgery due to pulmonary embolism.

Case 3: 77 year old women, underwent PDS, SCS 7, intraoperative estimated blood loss between 2 – 3 litres and had ileocaecal resection (faecal contamination of peritoneal cavity reported). The length of intensive care stay was for 6 days and

death was reported due to intra-abdominal sepsis on the 32nd day after surgery. Anastomosis leak or return to theatre for re-operation was not reported.

**Table 14: Intra-operative complications by SCS and timing of surgery in UK, India and overall cohort**

| Intra-operative complications | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Haemorrhage | Urinary tract injury | GI injury | Vascular injury | Anaesthetic complications | Total, n (%) |
| UK | | | | | | | |
| SCS type | Low (n=108) | 0 | 2 | 2 | 0 | 2 | 6 (5.6) |
| | Intermediate (n=53) | 0 | 2 | 1 | 2 | 0 | 5 (9.4) |
| | High (n=34) | 1 | 1 | 1 | 1 | 1 | 5 (14.7) |
| | Total (n=195) | 1 | 5 | 4 | 3 | 3 | 16 (8.2) |
| | | | | | | | |
| Timing of surgery | PDS (48) | 0 | 1 | 0 | 2 | 2 | 5 (10.4) |
| | NACT (147) | 1 | 4 | 4 | 1 | 1 | 11 (7.5) |
| | Total (n=195) | 1 | 5 | 4 | 3 | 3 | 16 (8.2) |
| India | | | | | | | |
| SCS type | Low (n=5) | 0 | 0 | 0 | 1 | 0 | 1(20) |
| | Intermediate (n=17) | 0 | 0 | 0 | 0 | 1 | 1(5.9) |
| | High (n=30) | 0 | 0 | 1 | 1 | 0 | 2 (6.7) |
| | Total (n=52) | 0 | 0 | 1 | 2 | 1 | 4 (7.7) |
| | | | | | | | |
| Timing of surgery | PDS (n=27) | 0 | 0 | 1 | 1 | 1 | 3 (11.1) |
| | NACT (n=25) | 0 | 0 | 0 | 1 | 0 | 1 (4) |
| | Total (n=52) | 0 | 0 | 1 | 2 | 1 | 4 (7.7) |
| SOCQER-2 | | | | | | | |
| SCS type | Low (n=113) | 0 | 2 | 2 | 1 | 2 | 7 (6.2) |
| | Intermediate (n=70) | 0 | 2 | 1 | 2 | 1 | 6 (8.6) |
| | High (n=64) | 1 | 1 | 2 | 2 | 1 | 7 (10.9) |
| | Total (n=247) | 1 | 5 | 5 | 5 | 4 | 20 (8.1) |
| | | | | | | | |
| Timing of surgery | PDS (n=75) | 0 | 1 | 1 | 3 | 3 | 8 (10.7) |
| | NACT (n=172) | 1 | 4 | 4 | 2 | 1 | 12 (7) |
| | Total (n=247) | 1 | 5 | 5 | 5 | 4 | 20 (8.1) |

**Table 15: Post-operative complications by SCS and timing of surgery in UK, India and overall cohort**

| Post-operative complications | | | | | | |
|---|---|---|---|---|---|---|
| | | C-D class 2, conservative management, n (%) | C-D class 3, Radiological/surgical management without GA, n (%) | C-D class 4, ITU/Operative management under GA, n (%) | C-D class 5, Death, n (%) | Total, n (%) |
| **UK** | | | | | | |
| **SCS type** | **Low (n=108)** | 11 | 8 | 0 | 1 | 20 (18.5) |
| | **Intermediate (n=53)** | 5 | 5 | 0 | 1 | 11 (20.8) |
| | **High (n=34)** | 6 | 3 | 4 | 0 | 13 (38.2) |
| | **Total (n=195)** | 22 (11.3) | **16 (8.2)** | **4 (2.1)** | **2 (1)** | 44 (22.6) |
| | | | | | | |
| **Timing of surgery** | **PDS (n=48)** | 6 | 8 | 1 | 1 | 16 (33.3) |
| | **NACT (n=147)** | 16 | 8 | 3 | 1 | 28 (19) |
| | **Total (n=195)** | 22 (11.3) | **16 (8.2)** | **4 (2.1)** | **2 (1)** | 44 (22.6) |
| **India** | | | | | | |
| **SCS type** | **Low (n=5)** | 1 | 1 | 0 | 0 | 2 (40) |
| | **Intermediate (n=17)** | 4 | 1 | 1 | 1 | 7 (41.2) |
| | **High (n=30)** | 11 | 6 | 3 | 0 | 20 (66.7) |
| | **Total (n=52)** | 16 (30.8) | **8 (15.4)** | **4 (7.7)** | **1 (1.9)** | 29 (55.8) |
| | | | | | | |
| **Timing of surgery** | **PDS (n=27)** | 9 | 5 | 2 | 1 | 17 (63) |
| | **NACT (n=25)** | 7 | 3 | 2 | 0 | 12 (48) |
| | **Total (n=52)** | 16 (30.8) | **8 (15.4)** | **4 (7.7)** | **1 (1.9)** | 29 (55.8) |
| **SOCQER-2** | | | | | | |
| **SCS type** | **Low (n=113)** | 12 | 9 | 0 | 1 | 22 (19.5) |
| | **Intermediate (n=70)** | 9 | 6 | 1 | 2 | 18 (25.7) |
| | **High (n=64)** | 17 | 9 | 7 | 0 | 33 (51.6) |
| | **Total (n=247)** | 38 (15.4) | **24 (9.7)** | **8 (3.2)** | **3 (1.2)** | 73 (29.6) |
| | | | | | | |
| **Timing of surgery** | **PDS (n=75)** | 15 | 13 | 3 | 2 | 33 (44) |
| | **NACT (n=172)** | 23 | 11 | 5 | 1 | 40 (23.3) |
| | **Total (n=247)** | 38 (15.4) | **24 (9.7)** | **8 (3.2)** | **3 (1.2)** | 73 (29.6) |

**Table 16: Clavien-Dindo Grade 3, 4 & 5 complications by SCS group and timing of surgery**

| | | C-D class 3, Radiological/surgical management without GA, | C-D class 4, ITU/Operative management under GA, | C-D class 5, Death, | Total | |
|---|---|---|---|---|---|---|
| | | N (%) | N (%) | N (%) | N | % |
| **UK** | | | | | | |
| **SCS type** | Low (n=108) | 8 | 0 | 1 | 9 | 8.3 |
| | Intermediate (n=53) | 5 | 0 | 1 | 6 | 11.3 |
| | High (n=34) | 3 | 4 | 0 | 7 | 20.6 |
| | Total (n=195) | 16 (8.2) | 4 (2.1) | 2 (1) | 22 | 11.3 |
| | | | | | | |
| **Timing of surgery** | PDS (n=48) | 8 | 1 | 1 | 10 | 20.8 |
| | NACT (n=147) | 8 | 3 | 1 | 12 | 8.2 |
| | Total (n=195) | 16 (8.2) | 4 (2.1) | 2 (1) | 22 | 11.3 |
| **India** | | | | | | |
| **SCS type** | Low (n=5) | 1 | 0 | 0 | 1 | 20.0 |
| | Intermediate (n=17) | 1 | 1 | 1 | 3 | 17.6 |
| | High (n=30) | 6 | 3 | 0 | 9 | 30.0 |
| | Total (n=52) | 8 (15.4) | 4 (7.7) | 1 (1.9) | 13 | 25.0 |
| | | | | | | |
| **Timing of surgery** | PDS (n=27) | 5 | 2 | 1 | 8 | 29.6 |
| | NACT (n=25) | 3 | 2 | 0 | 5 | 20.0 |
| | Total (n=52) | 8 (15.4) | 4 (7.7) | 1 (1.9) | 13 | 25.0 |
| **SOCQER-2** | | | | | | |
| **SCS type** | Low (n=113) | 9 | 0 | 1 | 10 | 8.8 |
| | Intermediate (n=70) | 6 | 1 | 2 | 9 | 12.9 |
| | High (n=64) | 9 | 7 | 0 | 16 | 25.0 |
| | Total (n=247) | 24 (9.7) | 8 (3.2) | 3 (1.2) | 35 | 14.2 |
| | | | | | | |
| **Timing of surgery** | PDS (n=75) | 13 | 3 | 2 | 18 | 24.0 |
| | NACT (n=172) | 11 | 5 | 1 | 17 | 9.9 |
| | Total (n=247) | 24 (9.7) | 8 (3.2) | 3 (1.2) | 35 | 14.2 |

**Table 17: Details of total number of events by SCS type (Note: One patient may have more than one event, others mostly included minor e vents)**

| | Low SCS | Intermediate SCS | High SCS | Number of events |
|---|---|---|---|---|
| Primary haemorrhage requiring return to theatre within 24 hours | 0 | 1 | 1 | 2 |
| Secondary haemorrhage requiring blood transfusion | 0 | 0 | 4 | 4 |
| Secondary haemorrhage - requiring return to theatre | 0 | 1 | 0 | 1 |
| Abscess / haematoma - requiring drainage without GA | 1 | 1 | 0 | 2 |
| Abscess / haematoma - requiring drainage with GA | 1 | 0 | 0 | 1 |
| Wound breakdown requiring conservative management | 5 | 1 | 4 | 10 |
| Wound breakdown requiring surgical management | 1 | 1 | 4 | 6 |
| Lymphocyst / Lymphoedema requiring radiological drainage | 0 | 0 | 1 | 1 |
| Sepsis - requiring systemic antibiotics | 5 | 4 | 9 | 18 |
| Sepsis - requiring ITU admission | 0 | 1 | 2 | 3 |
| Sepsis - with single organ failure | 0 | 0 | 0 | 0 |
| Sepsis - with multiple organ failure | 0 | 2 | 0 | 2 |
| Anastomotic leak - conservative / surgical management | 0 | 0 | 1 | 1 |
| Ileus - conservative management including NG tube | 6 | 4 | 4 | 14 |
| Bladder - retention / dysfunction | 0 | 0 | 1 | 1 |
| DVT - confirmed and required therapeutic anticoagulation | 0 | 0 | 1 | 1 |
| PE - confirmed and required therapeutic anticoagulation | 0 | 2 | 0 | 2 |
| Cardiac - arrhythmias / infarction / failure | 1 | 1 | 1 | 3 |
| Respiratory - pneumonia / failure /effusion | 7 | 2 | 5 | 14 |
| Fistula - conservative / surgical management | 0 | 0 | 1 | 1 |
| Other - any other relevant complication or disability as a complication of surgery | 16 | 14 | 27 | 57 |
| Total reported number of events | 48 | 37 | 70 | 155 |

## Patient Reported Outcome measures (PROMs):

Tables 18 and 19 show mean QoL score and standard deviations for different domains of EORTC QLQ-C30 at each time point and report a p-value for differences between groups at 6 weeks post-surgery and at 12 months in patients with groups of patients according to surgical complexity score. The last column reports p values for F tests from the complete case repeated measures ANOVA for within group effects (i.e. over time) and between groups. A short description and interpretation of main findings are described for each component being examined as footnotes along with the Table. Figures 14 – 28 demonstrate these QoL scores as line graphs to provide a visual understanding of their trend and directions. The results of post hoc comparisons from the complete case analysis up to 12 months are summarised in Appendix SQR11, page 161.

The apparent differences in the QoL scores can be noted beyond 12 months post-surgery which could be less precise due to changes in the study population. This is because of attrition in the number of patients in each group related to either death or progression of disease. The rate of response from patients eligible to return PRO data in low SCS group of patient is considerably lower (69 % and 46%) than intermediate (100% and 84%) and high SCS group (100% and 100%) at 18 months and 24 months respectively. Therefore, a comparison between the SCS groups at 18 and 24 months is less precise, may be biased and should be considered with caution.

**Table 18: QoL in patients according to SCS as per EORTC QLQ-C30**

| EORTC QLQ C30 | Types of surgery | Pre-surgery | | | 6 weeks | | | 6 months | | | 12 months | | | 18 months | | | 24 months | | | P value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | |
| **Global QoL** | Low SCS | 98 | 65.1 | 21.7 | 98 | 59.9 | 19.5 | 93 | 69.9 | 19.8 | 57 | 72.2 | 20.5 | 39 | 72.6 | 17.9 | 20 | 71.7 | 22.7 | #<0.001 |
| | Intermediate SCS | 62 | 59.8 | 19.9 | 61 | 60.1 | 19.3 | 53 | 67.3 | 21.5 | 44 | 74.4 | 18.6 | 32 | 76.3 | 19.6 | 20 | 77.1 | 16.2 | ##0.539 |
| | High SCS | 59 | 58.1 | 22.2 | 56 | 60.1 | 18.9 | 52 | 66.5 | 20.1 | 38 | 73.5 | 16.9 | 29 | 64.9 | 18.6 | 16 | 66.1 | 24.8 | |
| | p | | | | | 0.986 | | | | | | 0.867 | | | | | | | | ### |
| **Functional QoL: Physical function** | Low SCS | 99 | 75.7 | 19.8 | 97 | 64.5 | 20.2 | 93 | 76.3 | 21.5 | 56 | 80.6 | 18.9 | 39 | 81.9 | 17.0 | 20 | 80.7 | 17.8 | #<0.001 |
| | Intermediate SCS | 60 | 74.0 | 23.1 | 59 | 67.8 | 18.0 | 54 | 73.2 | 17.6 | 45 | 77.9 | 20.8 | 32 | 83.5 | 18.5 | 22 | 87.3 | 14.5 | ##0.009 |
| | High SCS | 60 | 73.4 | 20.9 | 50 | 55.6 | 18.6 | 54 | 64.4 | 24.2 | 40 | 76.5 | 19.3 | 31 | 77.2 | 21.8 | 19 | 83.5 | 21.2 | |
| | p | | | | | 0.004 | | | 0.007 | | | 0.528 | | | | | | | | ### |
| **Functional QoL: Role function** | Low SCS | 99 | 66.5 | 29.0 | 99 | 45.1 | 27.5 | 94 | 70.7 | 27.4 | 57 | 80.1 | 25.1 | 39 | 83.8 | 23.4 | 20 | 75.8 | 32.2 | #<0.001 |
| | Intermediate SCS | 61 | 65.8 | 28.8 | 60 | 52.8 | 26.8 | 55 | 67.9 | 29.7 | 45 | 75.2 | 24.8 | 33 | 81.8 | 27.1 | 22 | 89.4 | 21.5 | ##0.070 |
| | High SCS | 59 | 64.7 | 27.9 | 57 | 39.2 | 23.9 | 56 | 60.7 | 33.7 | 40 | 69.6 | 29.5 | 31 | 71.5 | 25.9 | 19 | 72.8 | 30.0 | |
| | p | | | | | 0.016 | | | | | | 0.166 | | | | | | | | ### |
| **Functional QoL: Emotional function** | Low SCS | 98 | 78.1 | 21.1 | 98 | 76.8 | 21.4 | 93 | 79.7 | 20.6 | 56 | 78.6 | 22.2 | 39 | 76.7 | 20.9 | 20 | 78.8 | 19.0 | #0.430 |
| | Intermediate SCS | 62 | 63.7 | 27.2 | 61 | 72.4 | 20.8 | 55 | 75.8 | 19.7 | 44 | 75.4 | 19.0 | 33 | 80.8 | 21.6 | 22 | 79.2 | 21.5 | ##0.005 |
| | High SCS | 59 | 62.6 | 25.4 | 57 | 69.3 | 19.4 | 55 | 69.2 | 25.7 | 39 | 73.3 | 23.4 | 31 | 70.2 | 23.6 | 19 | 66.7 | 26.6 | |
| | p | | | | | 0.034 | | | 0.036 | | | 0.548 | | | | | | | | ### |
| **Functional QoL: Cognitive function** | Low SCS | 99 | 78.3 | 21.2 | 99 | 75.9 | 21.1 | 91 | 78.2 | 21.3 | 56 | 81.3 | 20.1 | 39 | 78.6 | 21.9 | 20 | 77.5 | 18.9 | #0.732 |
| | Intermediate SCS | 62 | 76.3 | 26.2 | 61 | 78.1 | 21.2 | 55 | 78.2 | 20.8 | 45 | 79.3 | 24.9 | 33 | 83.8 | 21.8 | 22 | 84.8 | 16.2 | ##0.731 |
| | High SCS | 60 | 76.7 | 24.0 | 57 | 76.0 | 19.2 | 56 | 76.5 | 25.0 | 40 | 81.7 | 22.6 | 31 | 77.4 | 20.0 | 19 | 74.6 | 26.3 | |
| | p | | | | | 0.672 | | | | | | 0.82 | | | | | | | | ### |
| **Functional QoL: Social function** | Low SCS | 98 | 65.1 | 29.4 | 98 | 58.8 | 28.1 | 93 | 74.9 | 26.1 | 56 | 84.5 | 22.2 | 39 | 87.6 | 21.9 | 20 | 81.7 | 28.6 | #<0.001 |
| | Intermediate SCS | 61 | 58.7 | 29.9 | 59 | 60.5 | 26.2 | 55 | 71.5 | 31.5 | 45 | 83.0 | 21.8 | 33 | 85.9 | 24.0 | 21 | 81.7 | 23.5 | ##0.213 |
| | High SCS | 60 | 63.6 | 29.2 | 57 | 57.0 | 29.9 | 56 | 64.6 | 30.3 | 39 | 79.5 | 23.1 | 31 | 74.2 | 27.2 | 18 | 63.0 | 29.5 | |
| | p | | | | | 0.85 | | | | | | 0.481 | | | | | | | | ### |

[p-value represents complete case general linear repeated measures (one way ANOVA) at 12 months within the group (#) and in between the group (##). p-value in row (###) represents nonparametric (Kruskal-Wallis) test at a particular time point.]

**Findings (Table 18): Global QoL:** No statistical or clinically important difference in global QoL is present either at baseline or up to 12 months post-surgery. However, global QoL improved from baseline and from 6 weeks post-surgery with statistical and clinically important differences within the groups ($p<0.001$), but no differences between the groups at 12 months (Appendix SQR11, page 161). **Physical function:** No statistical or clinically important difference in physical function was present at baseline (pre-surgery) in between the groups. However, physical function was significantly and clinically worse in high SCS group ($p=0.004$) at 6 weeks post-surgery. At 6 months there was clinically important improvement in physical function in high SCS group, but it still remained statistically and clinically worse than low SCS group but similar to intermediate SCS group. After 6 months there were no differences among the groups. Statistical improvements and clinically important improvements in physical function were reported within all groups (Appendix SQR11). **Role function:** Statistically and clinically worse role function ($p=0.016$) was reported by patients with high SCS type at 6 weeks post-surgery. After 6 weeks there was statistical and clinically important improvement was present within each group. High SCS group patients were still clinically worse than low SCS group patients at 6 months and 12 months, but, no difference in role function was noted between intermediate and high SCS groups at 6 and 12 months (Appendix SQR11). **Emotional function:** Statistically and clinically worse emotional function scores were reported by patients undergoing high complexity surgery ($p=0.001$) at 6 weeks and 6 months post-surgery. No differences among study groups were reported at 12 months (Appendix SQR11). **Cognitive function:** No differences in cognitive function were reported by any group of patients at any time points under study. The cognitive function remained stable without showing any deterioration or any improvement within groups as well (Appendix SQR11). **Social function:** No differences in social functions were reported by any group of patient at any time points up to 12 months (Appendix SQR11).

The data are presented using line graphs below:

**Global QoL:**

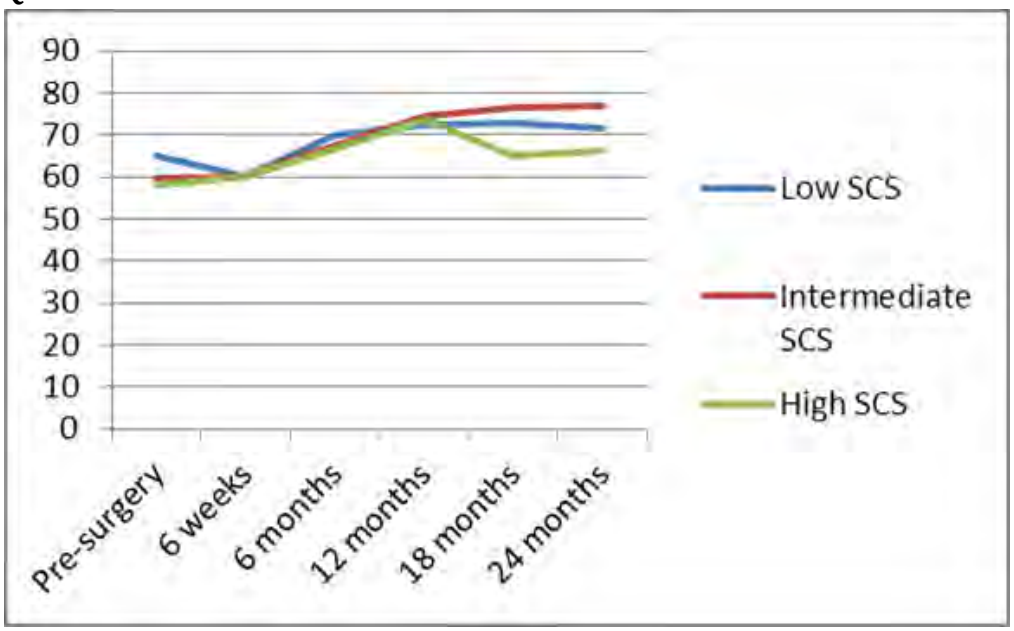



**Figure 14: EORTC QLQ-C30 Global QoL**

**Functional QoL: Physical function**

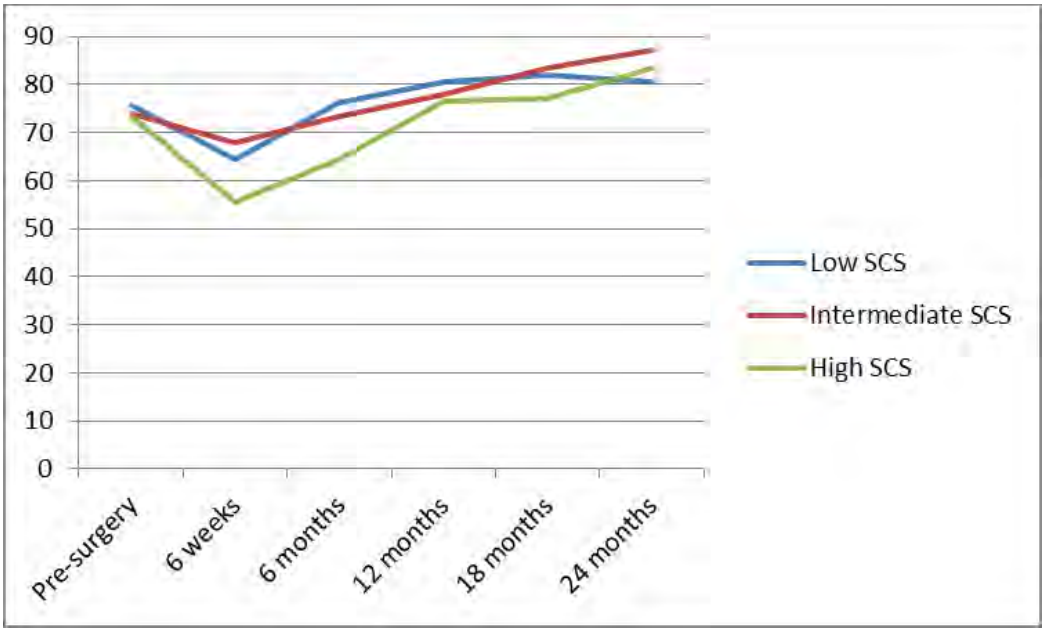



**Figure 15: EORTC QLQ-C30 Functional QoL - Physical function**

**Functional QoL: Role function**

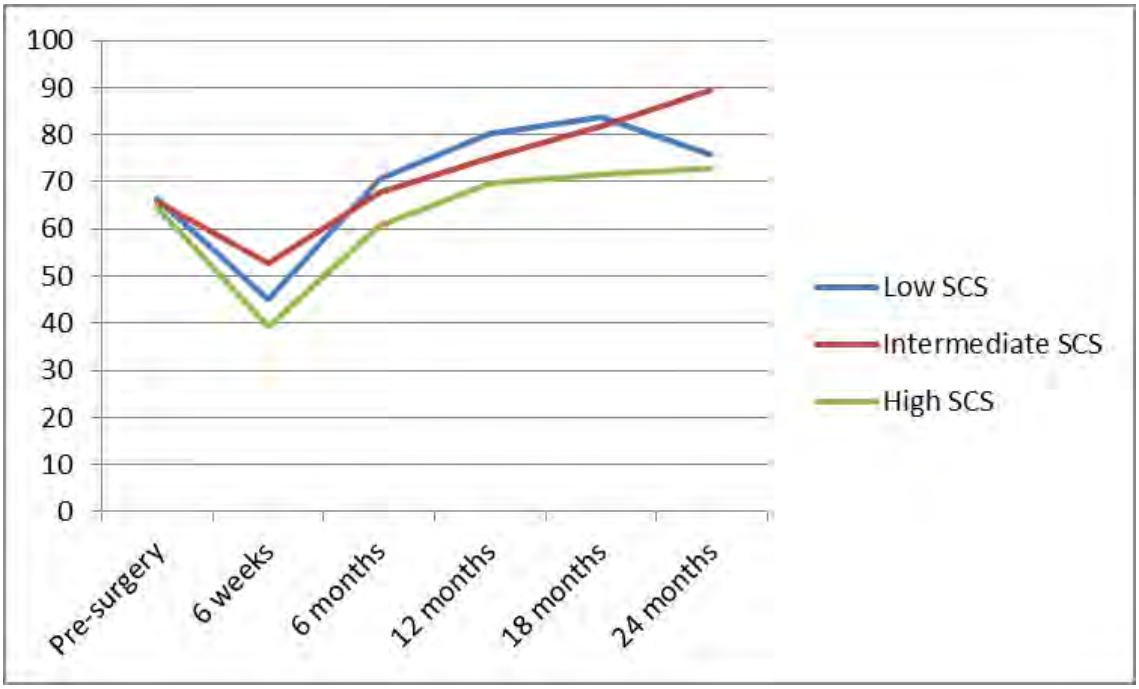



**Figure 16: EORTC QLQ-C30 Functional QoL - Role function**

**Functional QoL: Emotional function**

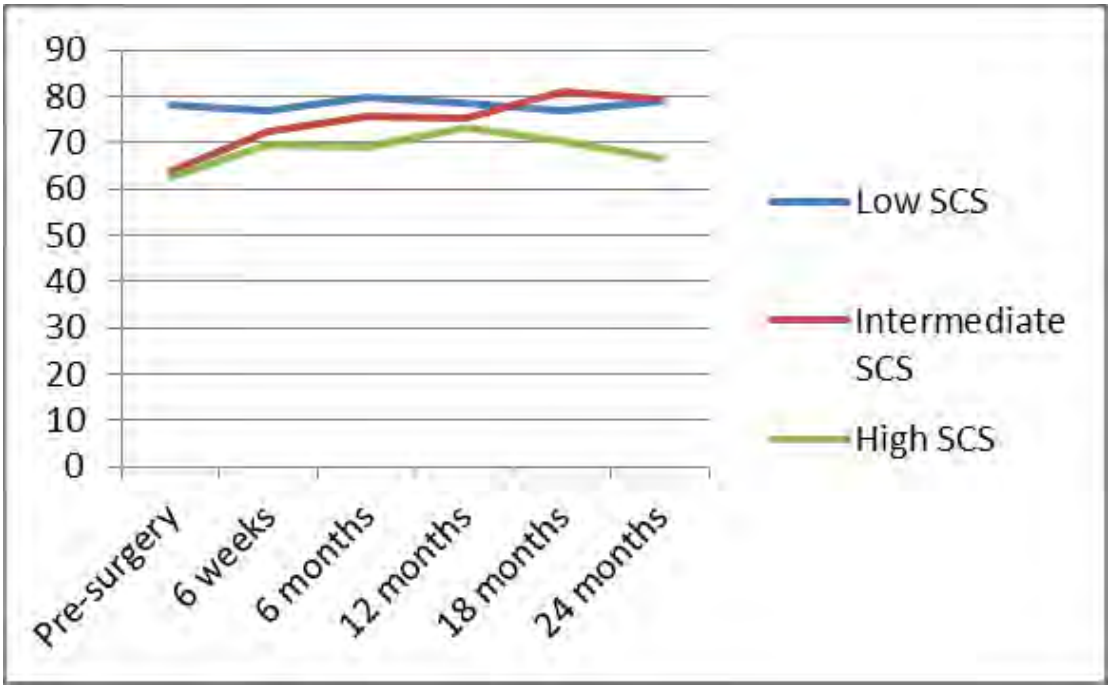



**Figure 17: EORTC QLQ-C30 Functional QoL - Emotional function**

**Functional QoL: Cognitive function**

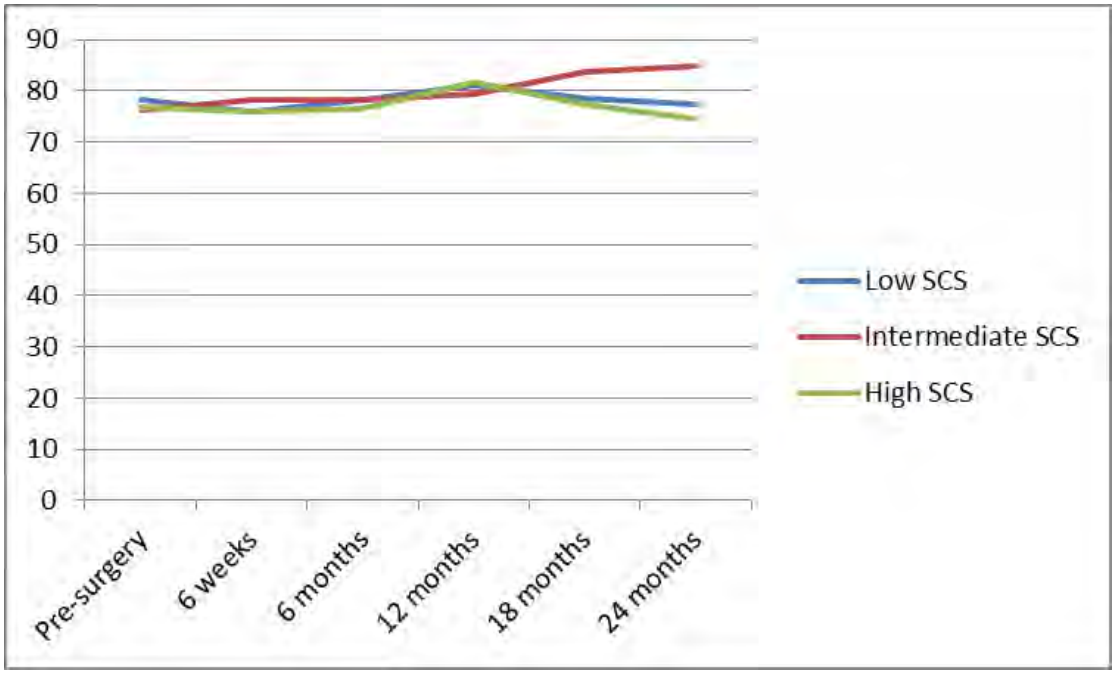



**Figure 18: EORTC QLQ-C30 Functional QoL - Cognitive function**

**Functional QoL: Social function:**

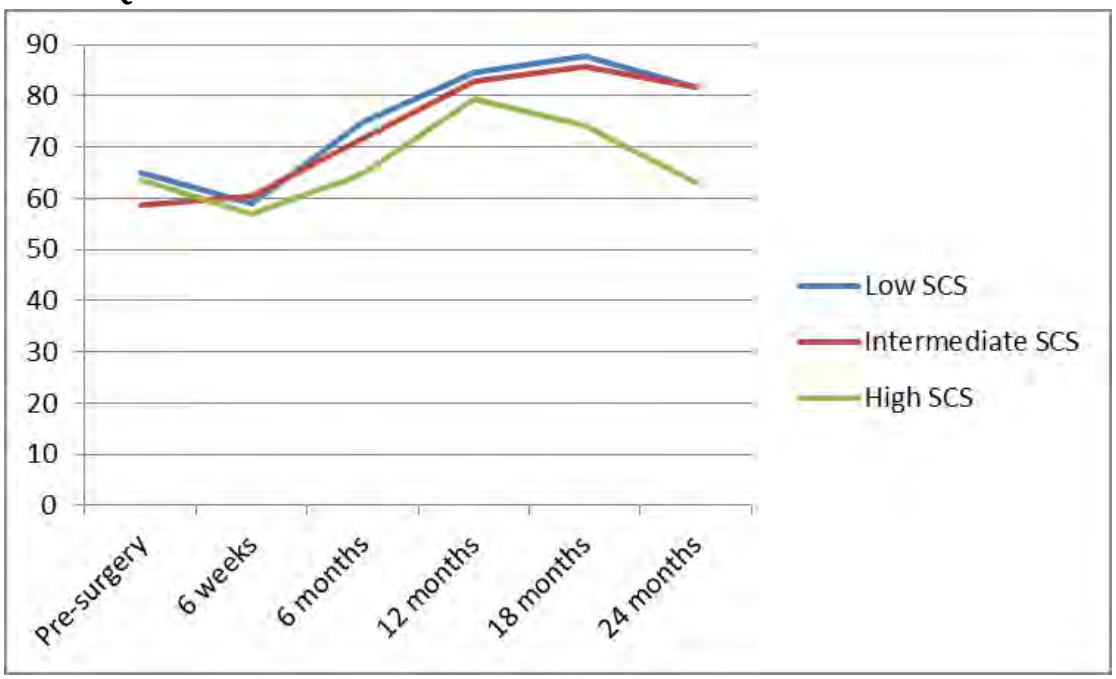



**Figure 19: EORTC QLQ-C30 Functional QoL - Social function**

**Table 19: EORTC QLQ-C30: Symptoms (Surgical complexity score)**

| EORTC QLQ C30 | Types of surgery | Pre-surgery | | | 6 weeks | | | 6 months | | | 12 months | | | 18 months | | | 24 months | | | P value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Symptom scale | | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | |
| FATIGUE | Low SCS | 96 | 38.3 | 22.9 | 99 | 51.1 | 23.5 | 93 | 33.1 | 24.7 | 57 | 28.9 | 22.2 | 39 | 30.2 | 21.5 | 20 | 31.1 | 26.9 | #<0.001 |
| | Intermediate SCS | 61 | 38.1 | 22.2 | 61 | 42.4 | 21.8 | 55 | 39.6 | 24.2 | 45 | 30.6 | 22.2 | 32 | 28.5 | 23.1 | 22 | 21.7 | 21.3 | ##0.798 |
| | High SCS | 60 | 36.5 | 21.5 | 57 | 49.1 | 21.3 | 56 | 40.7 | 27.8 | 40 | 26.7 | 20.9 | 31 | 27.6 | 25.8 | 19 | 22.2 | 28.5 | |
| | P | | | | | | **0.064** | | | | | | **0.682** | | | | | | | ### |
| NAUSEA | Low SCS | 99 | 8.2 | 19.4 | 98 | 14.1 | 21.2 | 93 | 7.5 | 16.8 | 57 | 8.2 | 16.4 | 39 | 4.7 | 10.1 | 20 | 5.0 | 10.9 | #0.030 |
| | Intermediate SCS | 59 | 14.7 | 24.4 | 60 | 13.9 | 19.2 | 55 | 11.5 | 23.1 | 45 | 10.7 | 21.4 | 33 | 8.6 | 16.2 | 22 | 9.8 | 16.0 | ##0.336 |
| | High SCS | 59 | 11.6 | 15.2 | 57 | 15.5 | 21.3 | 56 | 11.6 | 23.1 | 40 | 7.5 | 13.6 | 31 | 12.9 | 22.7 | 18 | 10.2 | 25.7 | |
| | P | | | | | | **0.997** | | | | | | **0.897** | | | | | | | ### |
| PAIN | Low SCS | 99 | 19.9 | 24.0 | 98 | 32.1 | 26.7 | 93 | 19.2 | 23.8 | 57 | 16.4 | 19.0 | 38 | 18.4 | 22.5 | 19 | 21.1 | 26.0 | #<0.001 |
| | Intermediate SCS | 61 | 26.2 | 27.1 | 61 | 28.1 | 24.4 | 55 | 28.5 | 27.0 | 45 | 22.2 | 26.1 | 33 | 15.7 | 22.8 | 22 | 12.1 | 18.7 | ##0.772 |
| | High SCS | 60 | 23.9 | 23.6 | 57 | 29.8 | 22.7 | 56 | 26.5 | 28.4 | 40 | 14.2 | 18.3 | 31 | 17.2 | 21.3 | 18 | 15.7 | 25.2 | |
| | P | | | | | | **0.6** | | | | | | **0.371** | | | | | | | ### |
| DYSPNOEA | Low SCS | 99 | 21.5 | 25.8 | 99 | 19.5 | 25.2 | 94 | 22.3 | 26.5 | 56 | 14.3 | 21.9 | 39 | 17.1 | 22.8 | 20 | 25.0 | 30.3 | #0.468 |
| | Intermediate SCS | 61 | 15.8 | 25.5 | 61 | 16.4 | 23.3 | 54 | 22.8 | 30.9 | 45 | 13.3 | 25.0 | 33 | 15.2 | 20.6 | 22 | 10.6 | 21.5 | ##0.837 |
| | High SCS | 60 | 17.8 | 20.8 | 57 | 18.1 | 27.5 | 56 | 17.9 | 23.8 | 40 | 15.8 | 21.3 | 31 | 18.3 | 24.1 | 19 | 12.3 | 19.9 | |
| | P | | | | | | **0.679** | | | | | | **0.611** | | | | | | | ### |
| INSOMNIA | Low SCS | 100 | 33.3 | 32.5 | 98 | 40.8 | 33.7 | 94 | 30.5 | 30.8 | 56 | 30.4 | 33.2 | 39 | 33.3 | 34.2 | 20 | 28.3 | 32.9 | #0.007 |
| | Intermediate SCS | 61 | 36.1 | 31.8 | 58 | 39.7 | 33.9 | 54 | 35.2 | 31.3 | 45 | 27.4 | 27.8 | 33 | 19.2 | 26.4 | 22 | 16.7 | 24.7 | ##0.812 |

| EORTC QLQ C30 | Types of surgery | Pre-surgery | | | 6 weeks | | | 6 months | | | 12 months | | | 18 months | | | 24 months | | | P value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Symptom scale | | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | |
| | High SCS | 60 | 35.6 | 32.4 | 57 | 36.3 | 31.7 | 56 | 32.7 | 32.7 | 40 | 25.8 | 29.7 | 31 | 31.2 | 36.4 | 19 | 35.1 | 36.0 | |
| | P | | | | | | **0.752** | | | | | | **0.843** | | | | | | | ### |
| **APPETITE** | Low SCS | 100 | 20.3 | 27.6 | 99 | 33.0 | 29.5 | 94 | 15.6 | 25.7 | 57 | 15.8 | 25.3 | 39 | 11.1 | 20.7 | 20 | 8.3 | 14.8 | #<0.001 |
| | Intermediate SCS | 61 | 31.1 | 32.7 | 61 | 25.7 | 28.8 | 55 | 13.9 | 24.6 | 45 | 10.4 | 22.3 | 33 | 10.1 | 24.3 | 22 | 7.6 | 17.6 | ##0.208 |
| | High SCS | 60 | 31.7 | 31.5 | 57 | 33.9 | 32.4 | 56 | 23.8 | 31.6 | 40 | 7.5 | 19.2 | 31 | 16.1 | 30.9 | 19 | 19.3 | 33.9 | |
| | P | | | | | | **0.24** | | | | | | **0.093** | | | | | | | ### |
| **CONSTIPATION** | Low SCS | 100 | 20.3 | 26.8 | 99 | 37.0 | 34.6 | 94 | 15.6 | 24.3 | 56 | 20.8 | 28.8 | 39 | 14.5 | 21.4 | 19 | 12.3 | 19.9 | #<0.001 |
| | Intermediate SCS | 61 | 24.0 | 29.3 | 61 | 37.7 | 33.6 | 55 | 21.8 | 30.2 | 45 | 16.3 | 25.2 | 33 | 23.2 | 31.7 | 22 | 18.2 | 24.6 | ##0.556 |
| | High SCS | 59 | 26.0 | 31.6 | 57 | 35.7 | 33.8 | 56 | 23.2 | 33.6 | 40 | 17.5 | 26.1 | 31 | 20.4 | 29.4 | 18 | 22.2 | 28.0 | |
| | P | | | | | | **0.947** | | | | | | **0.716** | | | | | | | ### |
| **DIARRHOEA** | Low SCS | 98 | 10.5 | 22.2 | 98 | 10.2 | 18.2 | 94 | 7.8 | 17.2 | 57 | 8.8 | 18.4 | 39 | 7.7 | 20.9 | 18 | 1.9 | 7.9 | #0.079 |
| | Intermediate SCS | 62 | 11.3 | 23.3 | 61 | 13.1 | 23.0 | 55 | 12.1 | 23.5 | 45 | 7.4 | 15.7 | 33 | 11.1 | 24.5 | 22 | 4.5 | 11.7 | ##0.204 |
| | High SCS | 59 | 10.2 | 21.7 | 57 | 17.5 | 26.8 | 55 | 12.7 | 20.8 | 40 | 13.3 | 25.9 | 31 | 18.3 | 27.0 | 18 | 11.1 | 22.9 | |
| | P | | | | | | **0.292** | | | | | | **0.818** | | | | | | | ### |
| **FINANCIAL Difficulty** | Low SCS | 98 | 14.3 | 26.2 | 97 | 12.7 | 21.8 | 94 | 13.1 | 24.5 | 56 | 6.5 | 14.8 | 38 | 4.4 | 17.6 | 20 | 1.7 | 7.5 | #0.103 |
| | Intermediate SCS | 62 | 31.2 | 35.6 | 60 | 24.4 | 34.1 | 55 | 27.3 | 35.2 | 44 | 18.2 | 26.4 | 33 | 10.1 | 22.8 | 22 | 16.7 | 26.7 | ##0.002 |
| | High SCS | 59 | 21.5 | 33.8 | 57 | 26.3 | 35.5 | 56 | 21.4 | 32.7 | 40 | 22.5 | 29.6 | 31 | 28.0 | 29.9 | 19 | 31.6 | 30.4 | |
| | P | | | **0.004** | | | **0.062** | | | **0.031** | | | **0.005** | | | **0.001** | | | **0.001** | ### |

[p value complete case general linear repeated measures (one way ANOVA) at 12 months within group (#), in between groups (##) and non-parametric (Kruskal-Wallis) test (###) in between group at given time point].

**Fatigue:**

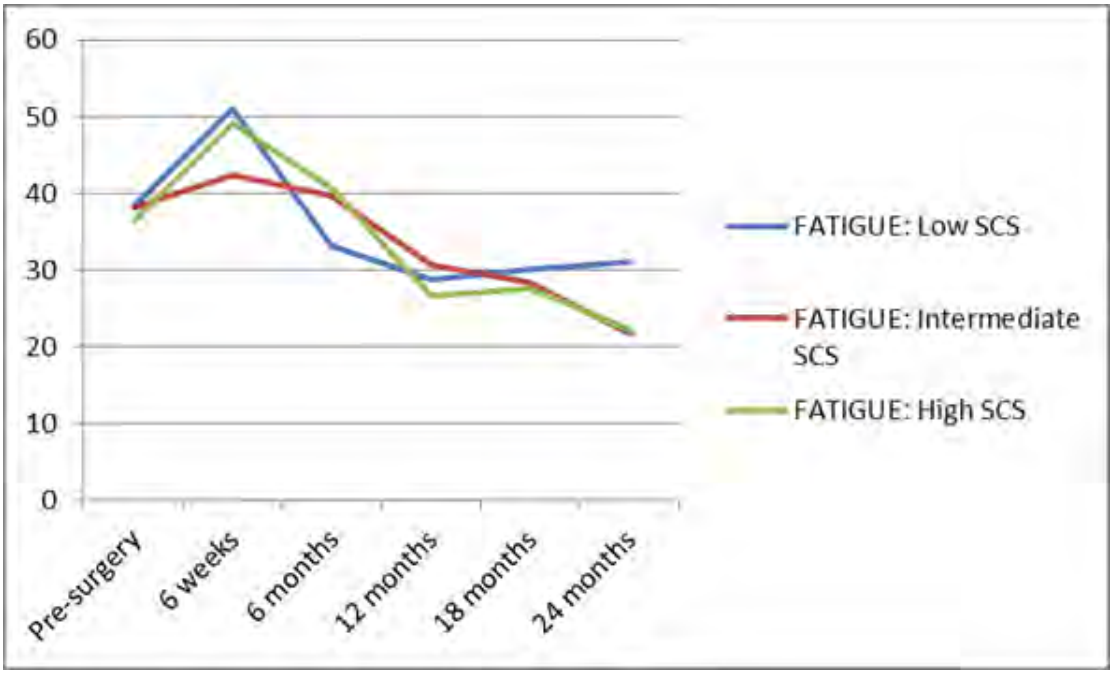



**Figure 20: EORTC QLQ-C30 Symptoms - Fatigue**

**Nausea:**

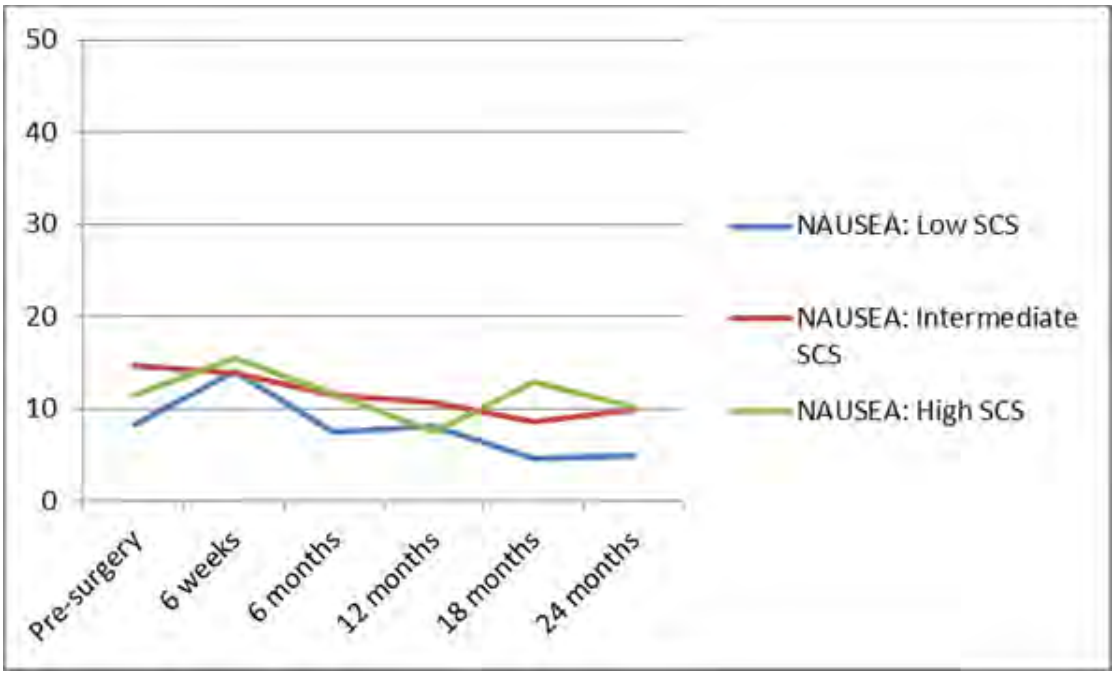



**Figure 21: EORTC QLQ-C30 Symptoms - Nausea**

**Pain:**

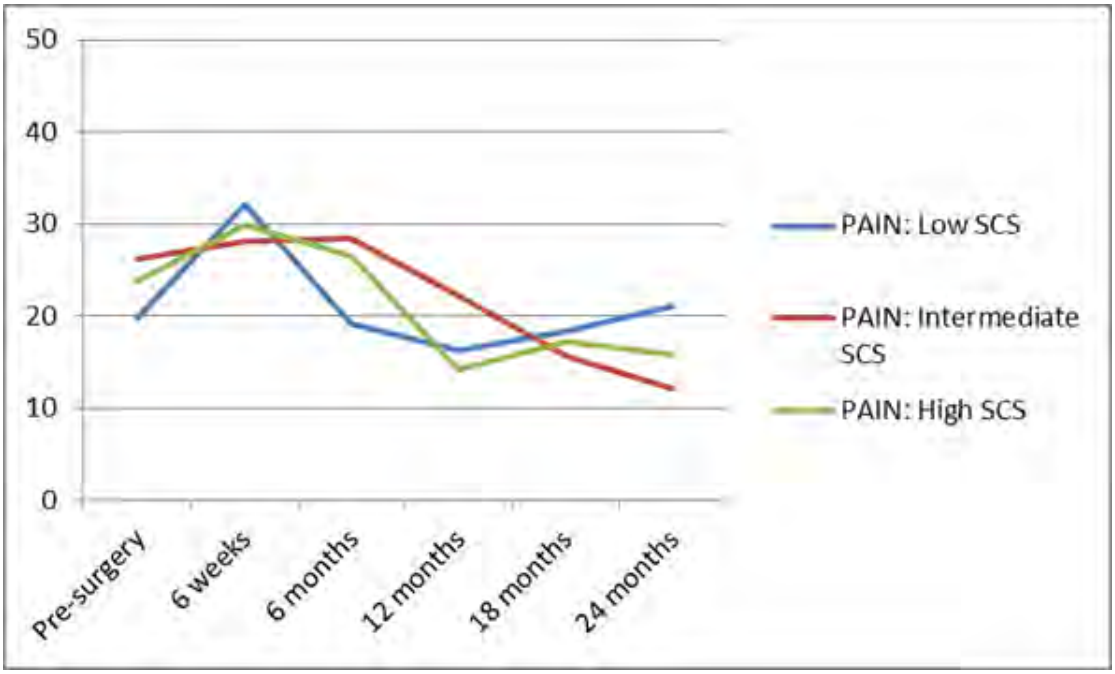



**Figure 22: EORTC QLQ-C30 Symptoms - Pain**

**Dyspnoea:**

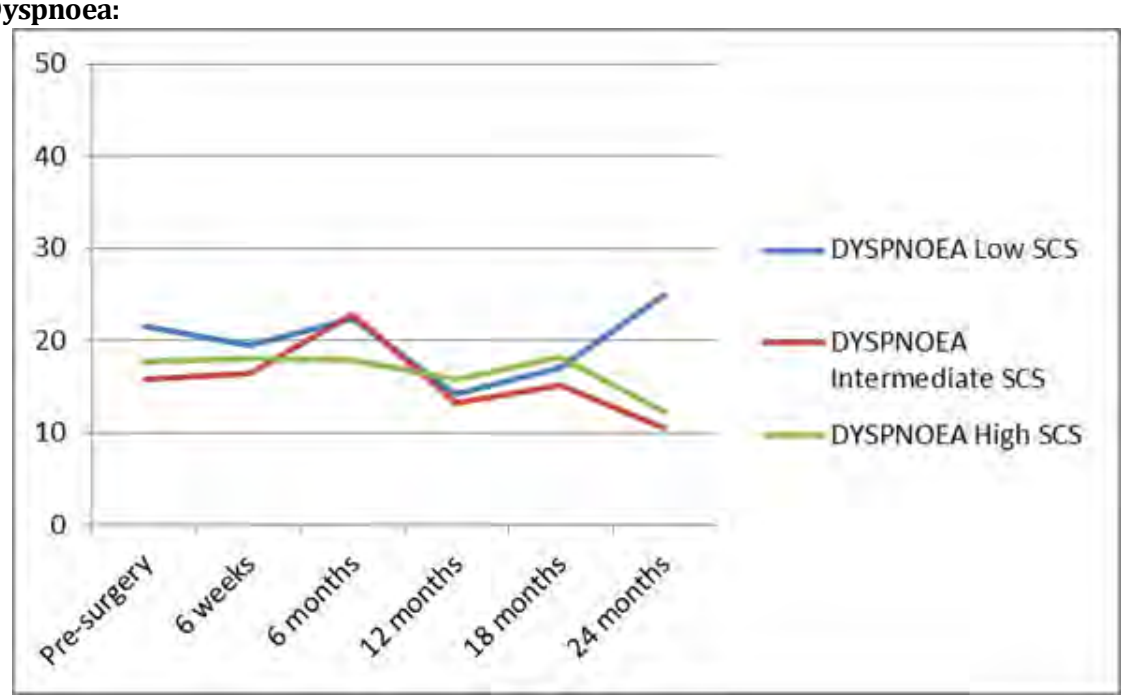



**Figure 23: EORTC QLQ-C30 Symptoms - Dyspnoea**

**Insomnia:**

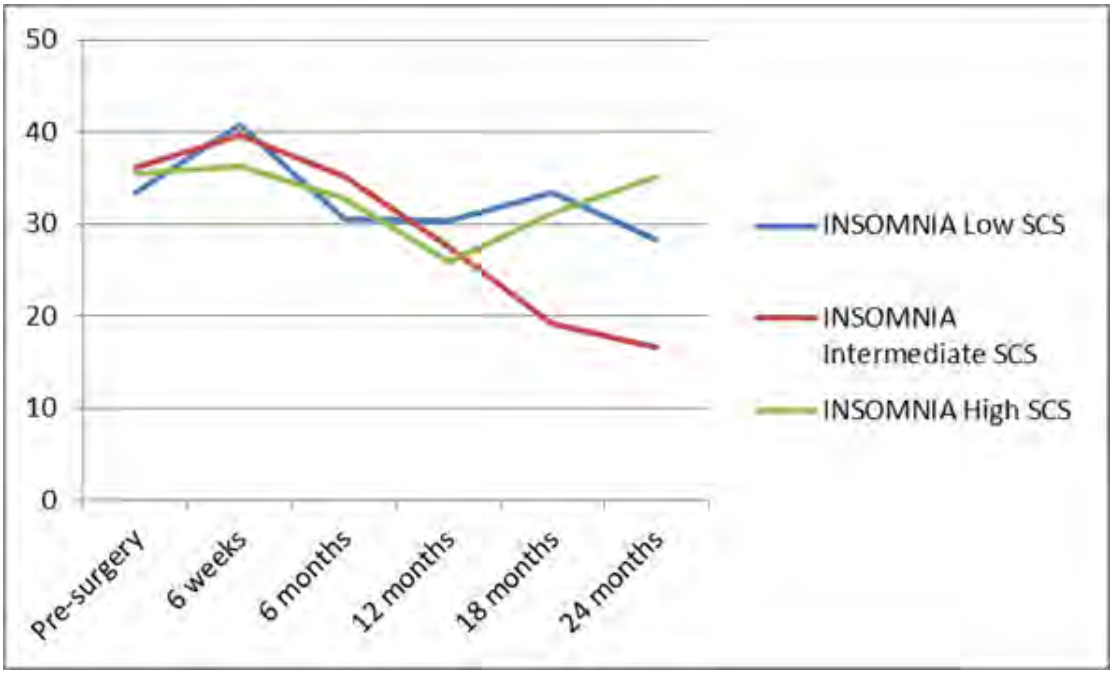



**Figure 24: EORTC QLQ-C30 Symptoms - Insomnia**

**Appetite:**

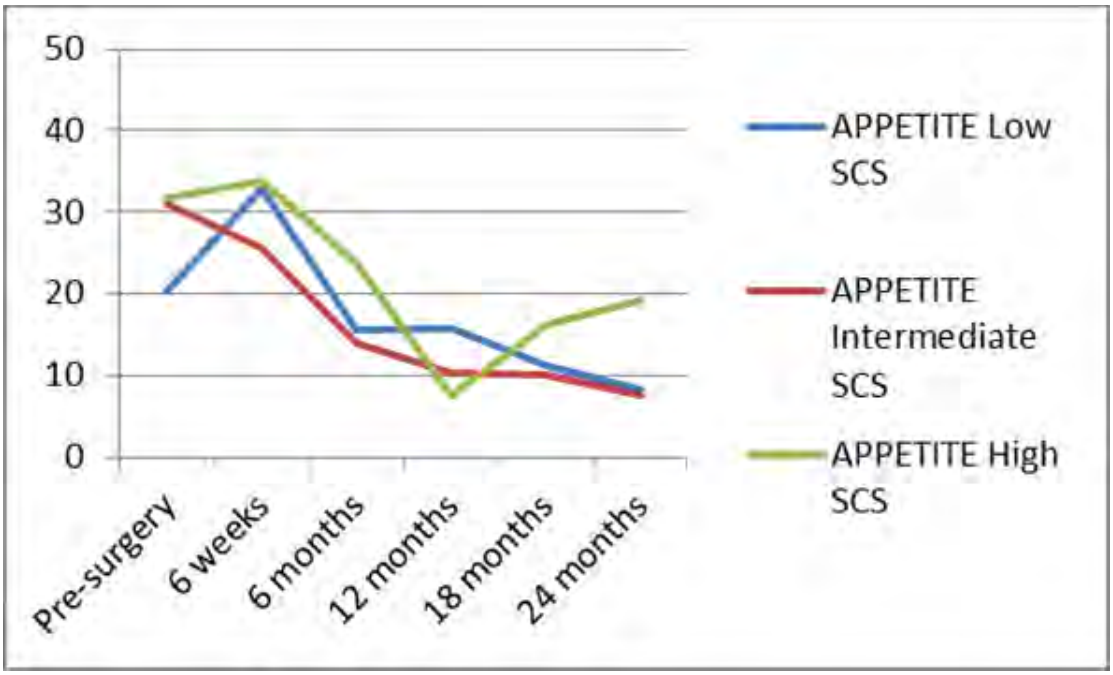



**Figure 25: EORTC QLQ-C30 Symptoms - Appetite**

**Constipation:**

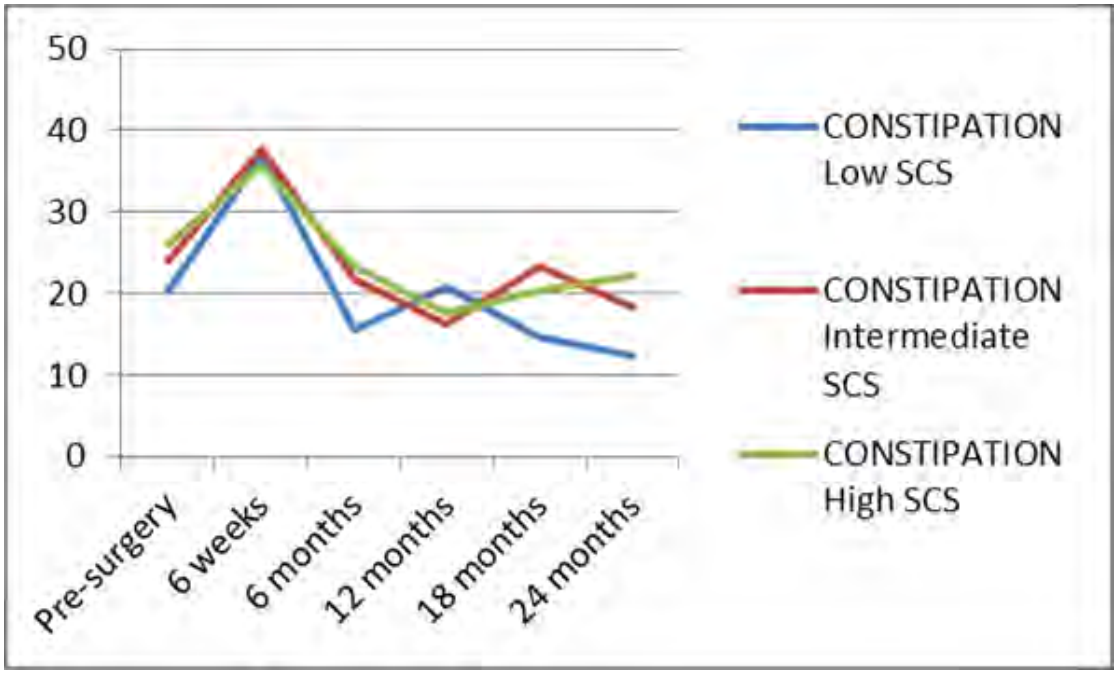



**Figure 26: EORTC QLQ-C30 Symptoms - Constipation**

**Diarrhoea:**

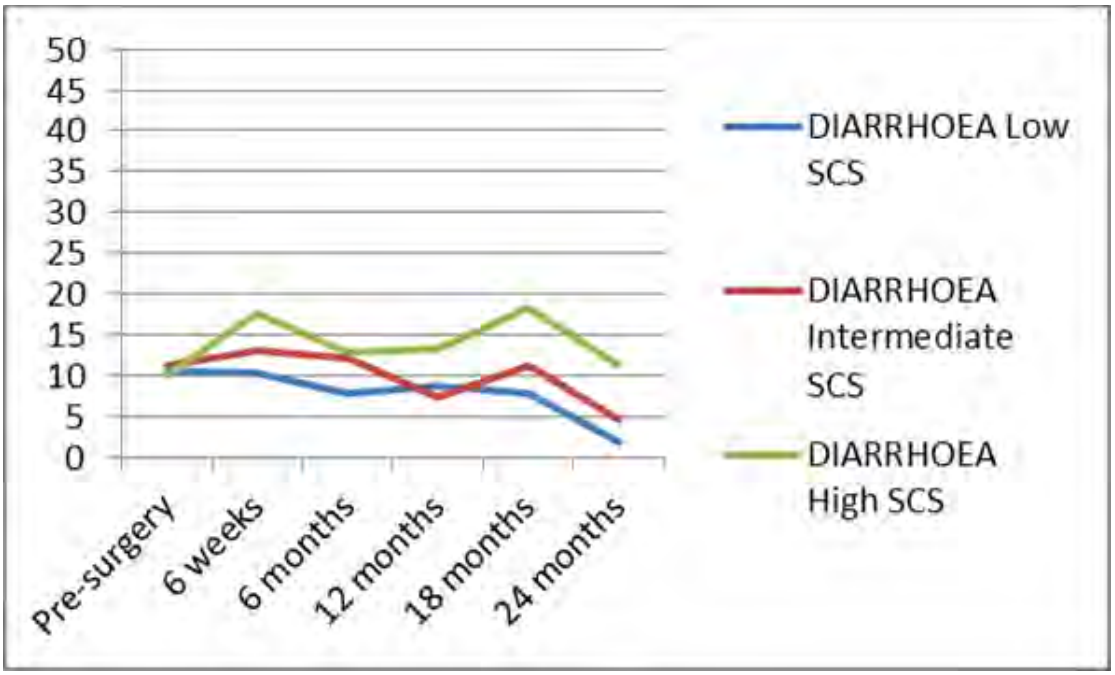



**Figure 27: EORTC QLQ-C30 Symptoms - Diarrhoea**

**Financial difficulty:**

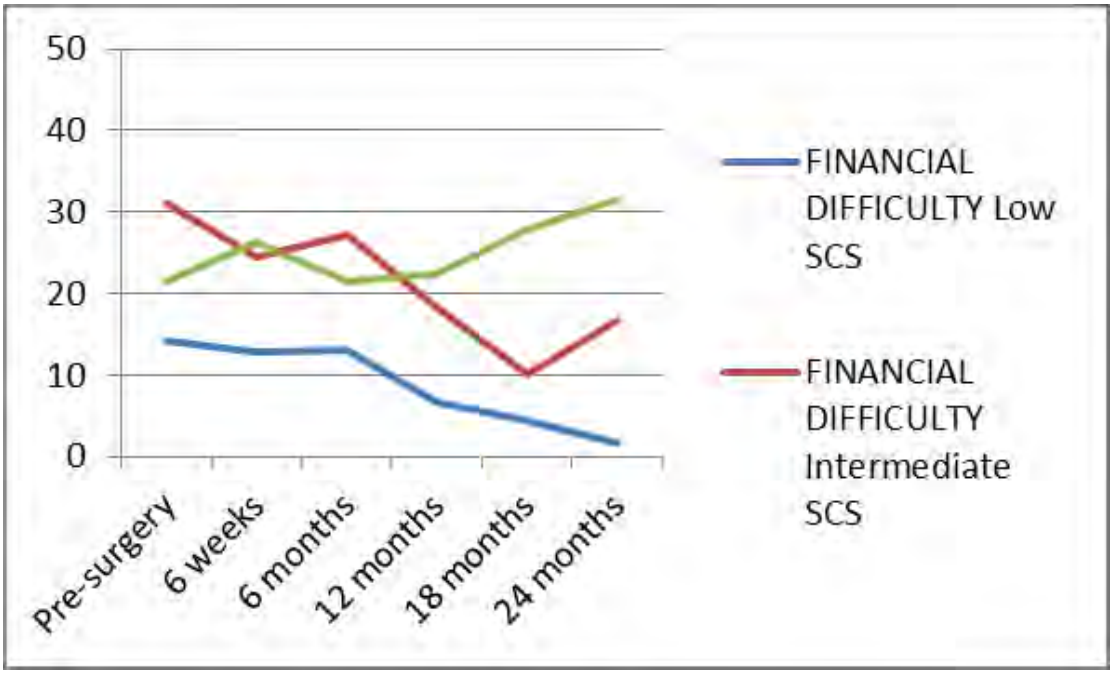



**Figure 28: EORTC QLQ-C30 Symptoms - Financial difficulty**

**Findings:** Preoperatively nausea and loss of appetite were worse symptoms for higher SCS type of patients. No major statistical or clinically important differences were observed in between the groups at any given time points post-operatively up to 12 months except for financial problems for higher SCS type groups, which were present prior to surgery and remained significant post-surgery (Appendix SQR11, page 161).

## EORTC QLQ-OV28 results by SCS type:

No difference in the QoL were reported by patients having debulking surgeries with different surgical complexity scores as per EORTC QLQ-OV28 at any given points except body image was reported to be worse by patients having high SCS at 18 months post-surgery (Table 20). Complete case analysis of all patients up to 12 months post-surgery shows that even though there was improvement in reported symptoms, it was statistically significant for abdominal pain and peripheral neuropathy within the treatment groups but no difference was present in between the treatment groups (Appendix SQR11, page 161).

Visually, in the OV28 scale, it can be observed in the line graphs (Figure 29 to 34) that abdominal pain and attitude to disease improve after 6 weeks but not to the level of clinically important difference. Hormonal symptoms and chemotherapy side effects either remains same or worse but not statistically or clinically important. Peripheral neuropathy remains clinically and statistically worse symptom at 6 months and 12 months in comparison to the baseline and 6 weeks post-surgery scores. No statistical or clinical difference was present in between the groups at any given time point up to 12 months (Table 21 and Appendix SQR11).

**Table 20: EORTC QLQ-OV28 results by SCS type**

| EORTC QLQ OV28 | Types of surgery | Pre-surgery | | | 6 weeks | | | 6 months | | | 12 months | | | 18 months | | | 24 months | | | P value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Symptom scale | | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | |
| **Abdominal pain** | Low SCS | 96 | 21.5 | 19.1 | 95 | 28.0 | 17.8 | 92 | 18.1 | 17.3 | 92 | 18.1 | 17.3 | 39 | 16.1 | 13.5 | 20 | 17.2 | 14.1 | #<0.001 |
| | Int. SCS | 62 | 32.7 | 26.3 | 60 | 29.3 | 20.7 | 55 | 24.0 | 22.6 | 55 | 24.0 | 22.6 | 33 | 15.8 | 20.1 | 22 | 14.1 | 17.4 | ##0.142 |
| | High SCS | 59 | 36.6 | 22.6 | 57 | 29.8 | 18.2 | 56 | 23.0 | 15.5 | 55 | 22.6 | 15.4 | 31 | 22.8 | 17.2 | 18 | 23.5 | 21.7 | |
| | P | | | | | **0.82** | | | | | | **0.091** | | | | | | | | ### |
| **Peripheral neuropathy** | Low SCS | 99 | 26.8 | 33.1 | 99 | 32.2 | 35.6 | 94 | 33.9 | 32.8 | 56 | 28.0 | 30.8 | 39 | 22.2 | 27.7 | 19 | 28.9 | 27.7 | #<0.001 |
| | Int. SCS | 60 | 17.2 | 29.4 | 61 | 25.4 | 32.1 | 53 | 39.6 | 33.2 | 45 | 34.8 | 35.3 | 33 | 28.8 | 26.1 | 22 | 21.2 | 23.1 | ##0.837 |
| | High SCS | 59 | 9.3 | 18.6 | 57 | 14.9 | 20.3 | 56 | 42.0 | 32.9 | 40 | 32.9 | 32.4 | 31 | 31.2 | 29.1 | 19 | 31.6 | 30.9 | |
| | P | | | | | **0.021** | | | | | | **0.61** | | | | | | | | ### |
| **Hormonal symptoms** | Low SCS | 99 | 20.2 | 27.8 | 99 | 24.6 | 28.8 | 94 | 24.3 | 32.5 | 57 | 24.6 | 30.2 | 39 | 23.5 | 27.2 | 20 | 20.0 | 28.4 | #0.067 |
| | Int. SCS | 62 | 23.9 | 32.9 | 61 | 29.5 | 33.0 | 54 | 30.6 | 33.8 | 44 | 26.9 | 29.2 | 33 | 24.2 | 24.0 | 22 | 18.9 | 20.8 | ##0.525 |
| | High SCS | 59 | 15.8 | 25.8 | 57 | 12.3 | 21.9 | 56 | 17.9 | 29.8 | 40 | 25.8 | 29.9 | 31 | 24.7 | 28.5 | 19 | 11.4 | 24.2 | |
| | P | | | | | **0.003** | | | | | | **0.847** | | | | | | | | ### |
| **Body image** | Low SCS | 97 | 32.6 | 27.1 | 99 | 38.0 | 25.5 | 94 | 32.1 | 25.9 | 57 | 25.7 | 28.7 | 39 | 17.1 | 21.1 | 20 | 18.3 | 25.9 | #0.001 |
| | Int. SCS | 62 | 34.9 | 24.1 | 59 | 39.8 | 30.5 | 54 | 34.6 | 32.4 | 45 | 32.2 | 28.3 | 33 | 15.7 | 27.3 | 22 | 22.0 | 27.4 | ##0.396 |
| | High SCS | 59 | 32.5 | 25.2 | 57 | 41.8 | 26.9 | 56 | 39.9 | 30.6 | 40 | 24.2 | 27.7 | 31 | 36.6 | 29.9 | 19 | 38.6 | 32.9 | |
| | P | | | | | **0.641** | | | | | | **0.235** | | | | | | | | ### |
| **Attitude to disease / treatment** | Low SCS | 95 | 48.2 | 25.0 | 99 | 52.7 | 25.7 | 93 | 44.6 | 29.6 | 56 | 37.3 | 24.8 | 39 | 29.3 | 24.5 | 20 | 33.3 | 29.5 | #0.001 |
| | Int. SCS | 60 | 55.4 | 25.3 | 59 | 53.3 | 24.7 | 54 | 49.4 | 30.8 | 45 | 44.7 | 27.6 | 33 | 29.6 | 23.5 | 22 | 31.8 | 23.3 | ##0.703 |
| | High SCS | 60 | 50.7 | 21.1 | 56 | 54.8 | 26.9 | 56 | 48.4 | 28.6 | 39 | 36.2 | 30.1 | 31 | 38.4 | 27.9 | 19 | 52.0 | 26.2 | |
| | P | | | | | **0.831** | | | | | | **0.306** | | | | | | | | ### |
| **Chemotherapy side effects** | Low SCS | 98 | 25.0 | 17.2 | 98 | 27.3 | 17.4 | 92 | 24.7 | 19.3 | 54 | 24.9 | 18.6 | 39 | 23.4 | 18.1 | 20 | 25.3 | 21.5 | #0.660 |
| | Int. SCS | 61 | 23.4 | 18.0 | 61 | 26.0 | 17.2 | 54 | 27.7 | 17.2 | 43 | 27.3 | 18.7 | 33 | 21.2 | 18.3 | 22 | 14.5 | 13.6 | ##0.491 |
| | High SCS | 59 | 17.9 | 14.9 | 57 | 21.2 | 13.5 | 56 | 23.3 | 13.9 | 39 | 20.9 | 15.2 | 31 | 20.2 | 17.3 | 19 | 17.2 | 19.2 | |
| | P | | | | | **0.092** | | | | | | **0.317** | | | | | | | | ### |
| **Other symptoms** | Low SCS | 71 | 42.4 | 20.5 | 67 | 50.7 | 19.0 | 38 | 41.0 | 23.4 | 15 | 31.1 | 21.7 | 10 | 24.2 | 17.8 | 5 | 20.0 | 15.1 | #0.004 |
| | Int. SCS | 34 | 44.6 | 26.3 | 37 | 42.8 | 22.4 | 37 | 42.3 | 20.0 | 20 | 30.4 | 25.8 | 19 | 21.1 | 21.4 | 12 | 16.7 | 20.1 | ##0.392 |
| | High SCS | 36 | 32.4 | 21.2 | 29 | 38.2 | 18.3 | 48 | 40.6 | 17.8 | 31 | 23.7 | 18.1 | 26 | 24.0 | 17.8 | 15 | 18.3 | 13.4 | |

| EORTC QLQ OV28 | Types of surgery | Pre-surgery | | | 6 weeks | | | 6 months | | | 12 months | | | 18 months | | | 24 months | | | P value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Symptom scale | | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | |
| | P | | | | **0.01** | | | | | | **0.482** | | | | | | | | | ### |

[p value complete case general linear repeated measures (one way ANOVA) at 12 months within group (#), in between groups (##) and non-parametric (Kruskal-Wallis) test (###) in between group at given time point]. N = Number, SD = Standard deviation, SCS = Surgical complexity score.

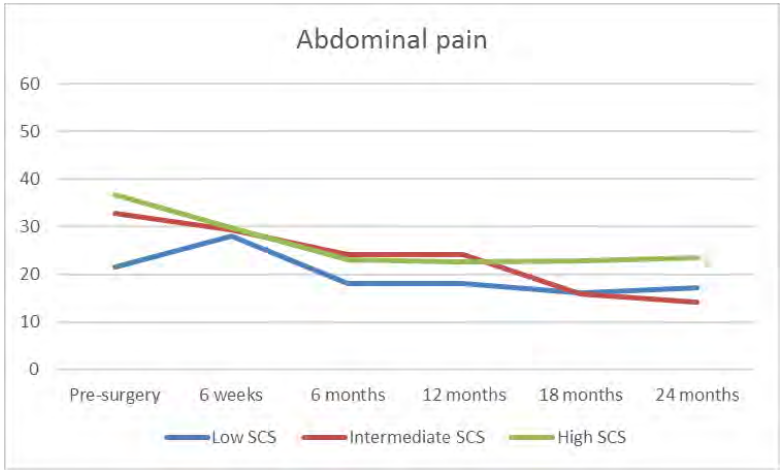



**Figure 30: EORTC QLQ-OV28 - Abdominal pain**

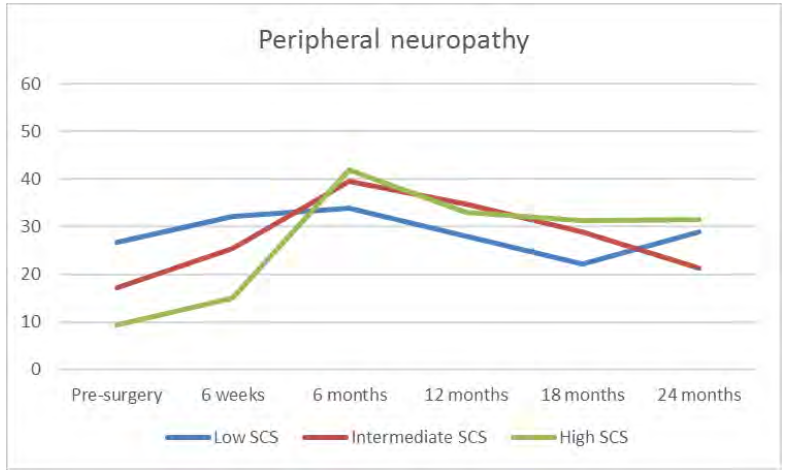



**Figure 29: EORTC QLQ-OV28 - Peripheral neuropathy**

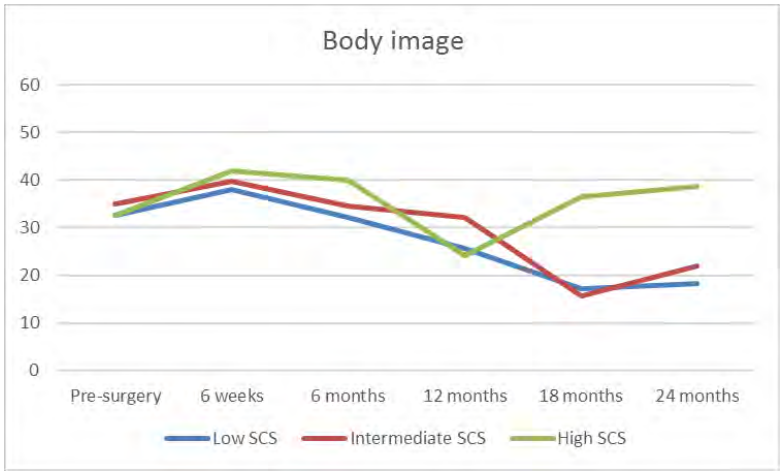



**Figure 33: EORTC QLQ-OV28 - Body image**

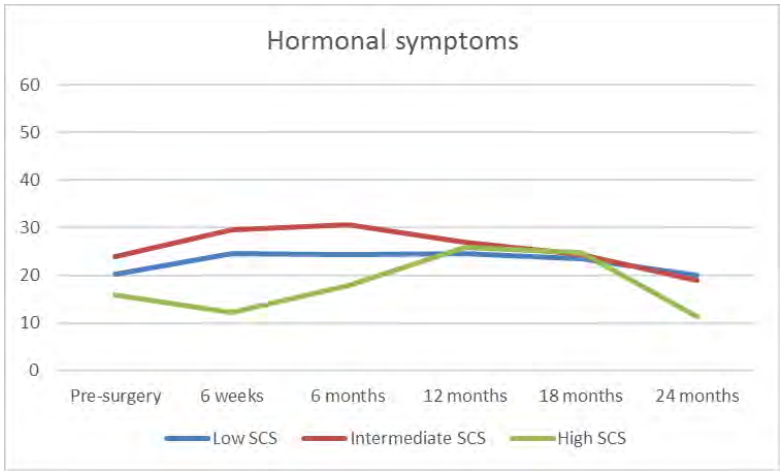



**Figure 34: EORTC QLQ-OV28 - Hormonal symptoms**

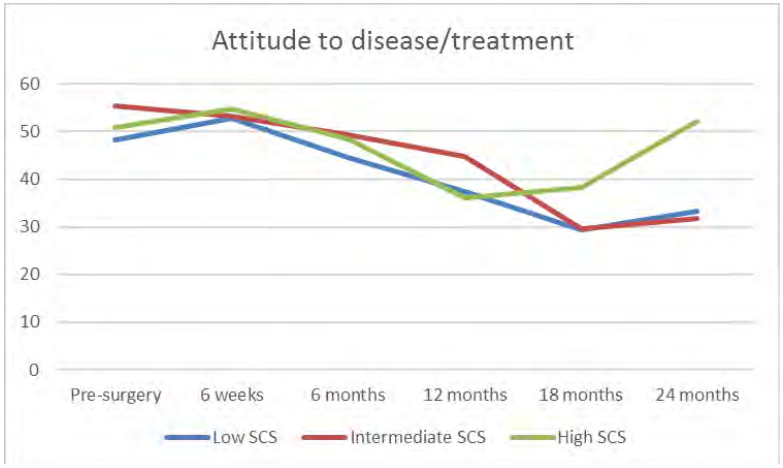



**Figure 31: EORTC QLQ-OV28 - Attitude to disease / treatment**

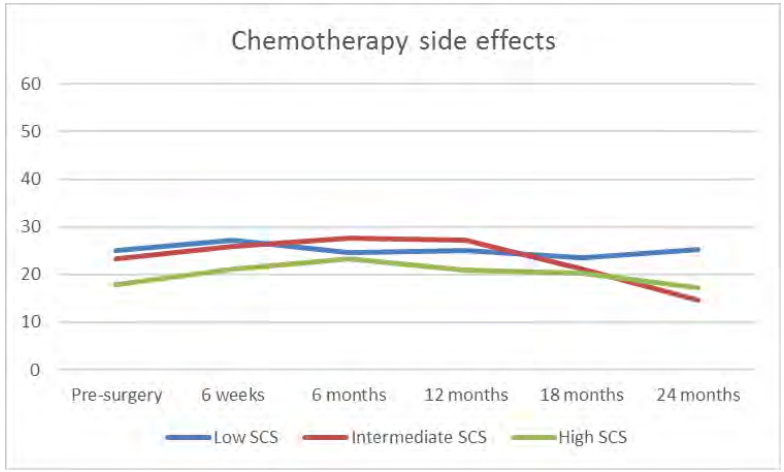



**Figure 32: EORTC QLQ-OV28 - Chemotherapy side effects**

**Summary of complete case analysis:** The analysis provides us three important results that can also be visualised through line graphs given with each item (Appendix SQR11, page 161).

1. Statistically significant differences in QoL may or may not translate into clinically important differences. However, in our cohort, these statistical significant changes are mostly in line with what is considered to be a clinically meaningful difference of 10 points.
2. It shows the time points where changes in QoL are statistically significant (contrasting between 6 weeks to 6 months, or 6 months to 12 months).
3. It points out the subgroups that have difference in QoL (if there are more than 2 dependent factors by performing between group post hoc comparisons with Bonferroni adjustment). However, the direction of impact is not shown by these p values, but demonstrated in the data table and in the line graphs.

**Findings by SCS type:** On EORTC QLQ-C30, global QoL, physical function, role function and social function improved ($p<0.001$) in all 3 groups of SCS category by 12 months post-surgery. These improvements were substantive between 6 weeks to 6 months, however, physical function continued to improve until 12 months. Patients with high SCS, reported statistically lower physical function ($p=0.009$) and emotional function ($p=0.005$) at 6 weeks to 6 months. Physical function of this group was still reported lower than low SCS group at 12 months ($p=0.001$). In other words, it can be said that, high SCS group reported lower QoL in physical and emotional function at 6 weeks and 6 months. However, emotional function improved to point of no difference by 6 months but physical function took 12

months to return to normal. Intermediate and high SCS group patients reported worse financial difficulty from the beginning that continued to be present at 12 months. An explanation of this is beyond the scope of this thesis; however, it could be either due to geographical location or related to lower (working) age group receiving high complexity surgeries. On OV28 symptoms scale, peripheral neuropathy (OV28) was the most commonly reported symptoms at 12 months in all patients. Emotional function, cognitive function, insomnia and dyspnoea did not show any marked improvement or deterioration within the group over time by 12 months.

As there were very limited differences between SCS groups, the impact of timing of surgery, disease burden and residual disease were explored in further analyses.

**Findings by timing of surgery (PDS vs NACT):** Improvements were reported by all groups for global QoL, physical function, role function and social function within the groups over all time points. However, the role and emotional function were lower for patients having primary debulking surgery at 6 weeks and improved to point of no difference by 6 months post-surgery. Peripheral neuropathy was worse in PDS group than NACT group at 6 months and 12 months, demonstrating the time lag in receiving chemotherapy between these 2 groups. Emotional function, cognitive function, insomnia and dyspnoea did not show any remarkable changes in any group of patients.

**Findings by disease burden (no upper abdominal disease vs upper abdominal disease):** No differences in QoL of patients were reported at any time-points up to 12 months. Improvements in other domains were consistent with

global, physical function, role function and social function. No effects were noted for emotional and cognitive function.

**Findings by residual disease status (no residual disease vs any residual disease):** No differences in QoL of patients were reported at any time-points up to 12 months. Improvements in other domains were consistent with global, physical function, role function and social function. No effects were noted for emotional and cognitive function. Statistically different but not clinically important differences were present in between the group for fatigue and insomnia. While fatigue was more commonly reported for patients with no residual disease (potentially due to higher complexity surgery), insomnia was more reported by patients with residual disease. However, these differences (8 points) did not reach to clinically meaningful differences (considered to be 10 point difference) and improved by 12 months. Peripheral neuropathy was commonly reported even at 12 months by both patient groups.

## Survival outcomes:

### Progression free survival

246/247 women (one withdrawal) were included in the analysis. Cumulative progression free survival at two years was 37.4%. PCI in low SCS and intermediate SCS groups were overlapping, therefore a comparison for PFS is presented for these 2 groups. PFS for high SCS group is also presented. The data demonstrates that with similar PCI, patients who have complete cytoreduction with intermediate SCS have better PFS and QoL. However, these differences were not statistically significant (Table 21 and Figure 35). Progression free survival varied with the level of disease, pre-operative PCI, ACCI (Charlson comorbidity score), residual disease and pre-operative albumin level, but did not show differences by age, initial treatment strategy (PDS or NACT) or country (Table 21). For progression free survival, the variables except for residual disease status as listed in Table 21 were included in a forward stepwise model and the final Cox proportional hazard model included ACCI and maximum level of disease only and not SCS (Table 22).

### Overall survival

Overall survival at two years was 76.0% (SE 2.7%). Overall survival was higher in patients who underwent surgery of intermediate complexity when compared to patients who had lower complexity surgery (p=.043) but similar for patients with high SCS and low SCS groups (Table 23 and Figure 37). Overall survival varied with the level of disease, pre-operative PCI, ACCI and with pre-operative albumin level, but did not show differences by age, initial treatment strategy or country. For overall survival, the variables except residual disease status as listed in Table 23 were included in a forward stepwise model and the final Cox proportional hazards

model included SCS, pre-operative albumin, ACCI and PCI (Table 24). When adjusted for pre-operative albumin, PCI and ACCI, low SCS compared with intermediate SCS was associated with a statistically significantly greater hazard of death, while an increased hazard for high SCS compared with intermediate SCS did not reach statistical significance (Table 24).

**Residual disease status:** Having no residual disease or any residual disease after the surgery is an outcome of surgical intervention and therefore it was not included in regression model as a predictor for survival. However, it is very much evident that patients achieving a no residual disease status after the surgery had a significantly better PFS (47.3% vs 21.1%, $p<0.001$) and OS (83.2% vs 64.4%, $p<0.001$) rate at the end of 2 years (Table 21, Figure 36, Table 23 and Figure 38).

**Table 21: Kaplan Meier cumulative progression free survival at 2 years**

| Categories | Characteristics | N | % PFS at 2 years | 95% CI | | p |
|---|---|---|---|---|---|---|
| Surgical complexity score | Low | 113 | 33.5 | 24.7 | 42.3 | 0.109 |
| | Intermediate | 70 | 46.8 | 35.0 | 58.6 | |
| | High | 64 | 34.2 | 22.4 | 46.0 | |
| Level of disease | Pelvic disease only | 27 | 55.6 | 36.8 | 74.4 | 0.001 |
| | Pelvic and mid-abdominal disease | 69 | 49.2 | 37.4 | 61.0 | |
| | Upper abdominal and other disease | 151 | 28.7 | 21.4 | 36.0 | |
| Pre-operative PCI | PCI <5 | 71 | 49.2 | 37.6 | 60.8 | 0.019 |
| | PCI 5-14 | 88 | 34.1 | 24.1 | 44.1 | |
| | PCI >=15 | 88 | 31.5 | 21.7 | 41.3 | |
| Pre-operative albumin | <35 | 53 | 28.9 | 16.4 | 41.4 | 0.040 |
| | >=35 | 193 | 48.7 | 41.6 | 55.8 | |
| Age | <65 | 143 | 41.8 | 33.8 | 49.8 | 0.169 |
| | >=65 | 103 | 30.7 | 21.7 | 39.7 | |
| ACCI | <=2 | 157 | 45.1 | 37.3 | 52.9 | 0.003 |
| | >=3 | 89 | 22.8 | 14.0 | 31.6 | |
| Residual disease status | No residual disease | 152 | 47.1 | 39.1 | 55.1 | <0.001 |
| | Any residual disease | 94 | 21.3 | 13.1 | 29.5 | |
| Timing of surgery | PDS | 75 | 46.4 | 35.0 | 57.8 | 0.291 |
| | NACT | 171 | 33.3 | 26.2 | 40.4 | |
| Location | UK patient | 194 | 36.8 | 29.9 | 43.7 | 0.898 |
| | India patient | 52 | 38.5 | 25.4 | 51.6 | |
| | All | 246 | 37.4 | 31.3 | 43.5 | |

**Table 22: Progression free survival adjusted hazard ratios**

| | B | SE | Wald | df | Sig. | Hazard ratio (Exp(B)) | 95.0% CI | |
|---|---|---|---|---|---|---|---|---|
| **ACCI >2** | 0.48 | 0.16 | 8.83 | 1 | 0.003 | 1.62 | 1.18 | 2.23 |
| **Pelvic disease only (reference)** | | | 13.82 | 2 | 0.001 | | | |
| **Pelvic and mid abdominal disease** | 0.29 | 0.34 | 0.76 | 1 | 0.384 | 1.34 | 0.69 | 2.58 |
| **Upper abdominal and other disease** | 0.85 | 0.31 | 7.79 | 1 | 0.005 | 2.34 | 1.29 | 4.26 |

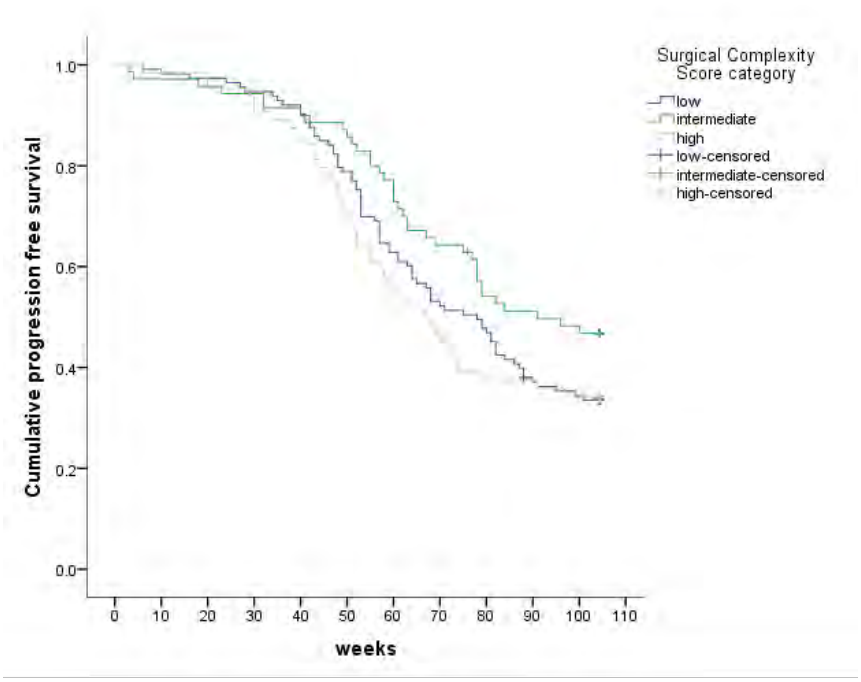



**Figure 35: Cumulative progression free survival by SCS type**

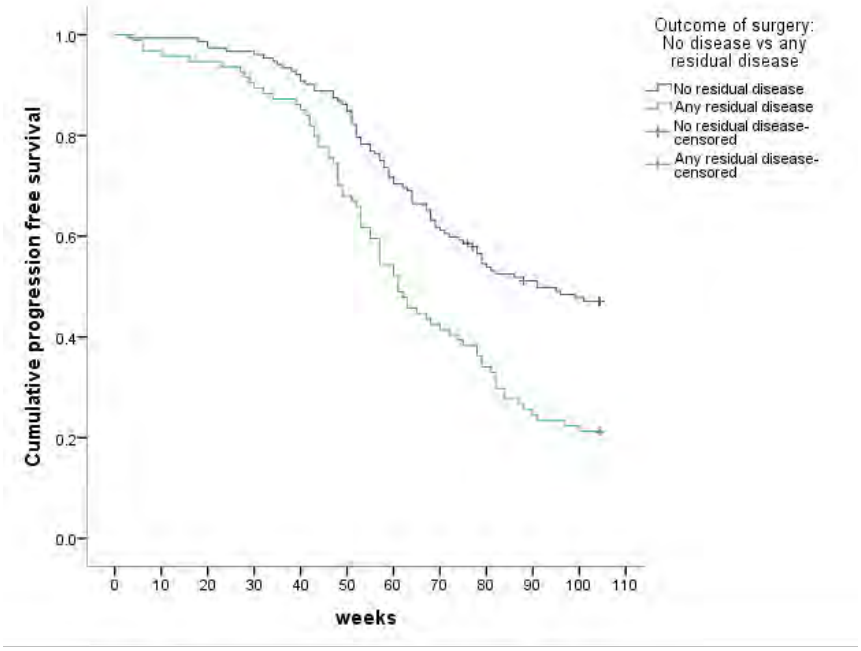



**Figure 36: Cumulative progression free survival by residual disease status**

**Table 23: Cumulative overall survival at 2 years in weeks**

| Categories | Characteristics | N | % OS 2 years | 95% CI | | P (log rank test) |
|---|---|---|---|---|---|---|
| Surgical complexity score | Low | 113 | 72.5 | 64.3 | 80.7 | 0.043 |
| | Intermediate | 70 | 87.1 | 79.3 | 94.9 | |
| | High | 64 | 70.1 | 58.7 | 81.5 | |
| Level of disease | Pelvic disease only | 27 | 81.5 | 66.8 | 96.2 | 0.048 |
| | Pelvic and mid-abdominal disease | 69 | 85.5 | 77.3 | 93.7 | |
| | Upper abdominal and other disease | 151 | 70.7 | 63.4 | 78.0 | |
| Pre-operative PCI | PCI <5 | 71 | 85.8 | 77.6 | 94.0 | 0.008 |
| | PCI 5-14 | 88 | 78.4 | 69.8 | 87.0 | |
| | PCI >=15 | 88 | 65.5 | 55.5 | 75.5 | |
| Pre-operative albumin | <35 | 53 | 58.0 | 44.7 | 71.3 | <.001 |
| | >=35 | 193 | 80.8 | 75.3 | 86.3 | |
| Age | <65 | 143 | 78.9 | 72.2 | 85.6 | .183 |
| | >=65 | 103 | 71.7 | 62.9 | 80.5 | |
| ACCI | <=2 | 157 | 82.7 | 76.8 | 88.6 | 0.001 |
| | >=3 | 89 | 63.7 | 53.7 | 73.7 | |
| Residual disease status | No residual disease | 152 | 83.4 | 77.5 | 89.3 | <0.001 |
| | Any residual disease | 94 | 64.2 | 54.6 | 73.8 | |
| Timing of surgery | PDS | 75 | 74.3 | 64.3 | 84.3 | .650 |
| | NACT | 171 | 76.6 | 70.3 | 82.9 | |
| Location | UK patient | 194 | 75.6 | 69.5 | 81.7 | .867 |
| | India patient | 52 | 76.9 | 65.5 | 88.3 | |
| | All | 247 | 76.0 | 70.7 | 81.3 | |

**Table 24: Overall survival adjusted hazard ratios**

| | B | SE | Wald | df | Sig. | Hazard ratio(Exp(B)) | 95.0% CI | |
|---|---|---|---|---|---|---|---|---|
| **Intermediate SCS (reference)** | | | 6.05 | 2 | 0.049 | | | |
| **Low SCS** | 0.94 | 0.39 | 5.8 | 1 | 0.016 | 2.56 | 1.19 | 5.50 |
| **High SCS** | 0.52 | 0.42 | 1.51 | 1 | 0.219 | 1.68 | 0.73 | 3.88 |
| **ACCI > 2** | 0.73 | 0.28 | 6.98 | 1 | 0.008 | 2.08 | 1.21 | 3.59 |
| **Pre-operative albumin <35g/l** | 0.69 | 0.29 | 5.83 | 1 | 0.016 | 2.00 | 1.14 | 3.50 |
| **Pre-operative PCI ≤5 (reference)** | | | 10.21 | 2 | 0.006 | | | |
| **Pre-operative PCI 6-14** | 0.78 | 0.40 | 3.79 | 1 | 0.052 | 2.18 | 0.99 | 4.79 |
| **Pre-operative PCI≥15** | 1.34 | 0.420 | 10.14 | 1 | 0.001 | 3.80 | 1.67 | 8.64 |

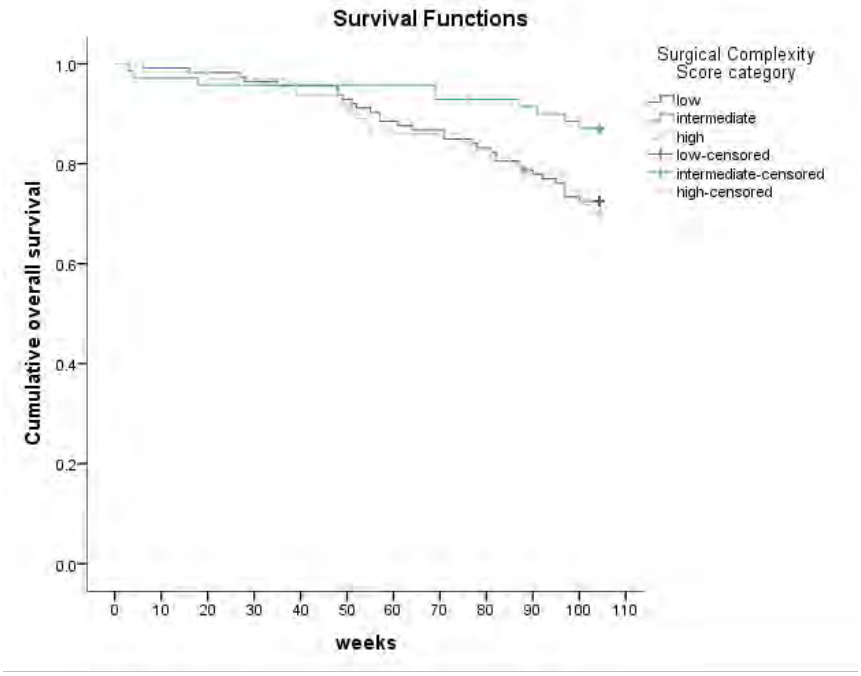



**Figure 37: Cumulative overall survival by SCS type at 2 years**

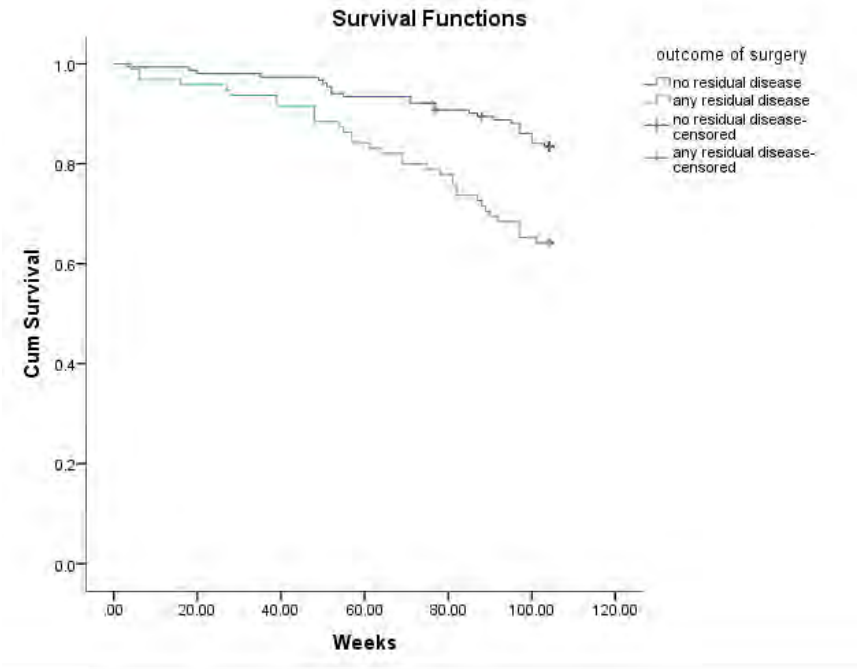



**Figure 38: Cumulative overall survival by residual disease status**

## Variations in patient characteristics by contributing centres:

We found evidence of differences in practice regarding surgical complexity and patient characteristics. This suggests differences in patient selection for surgery between centres. Figure 39 shows the pre-operative PCI recorded from different participating centres and Figure 40 shows the use of different types of surgical complexity surgery for advanced ovarian cancer. This evidence demonstrates differences in departmental policies for patient selection, treatment approach and utilisation of upper abdominal surgeries.

A key limitation is that the cases below, only represent patients recruited into SOCQER-2 study and may not fully capture the patients in each participating centre. The study team is conducting a denominator dataset analysis from national COSD data. This is beyond the scope of this thesis and will not be discussed.

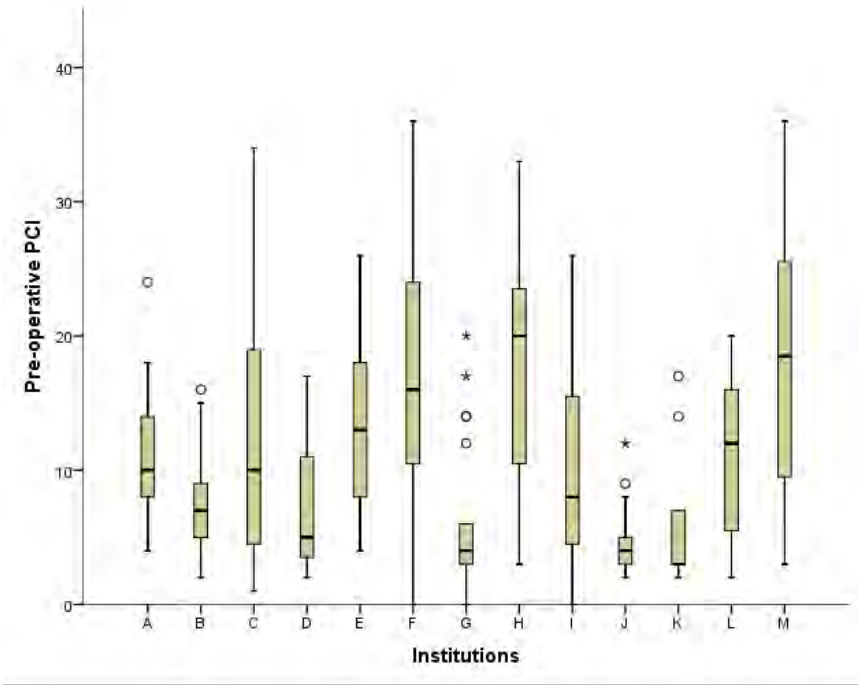



**Figure 39: Pre-operative PCI as observed in all institutions**

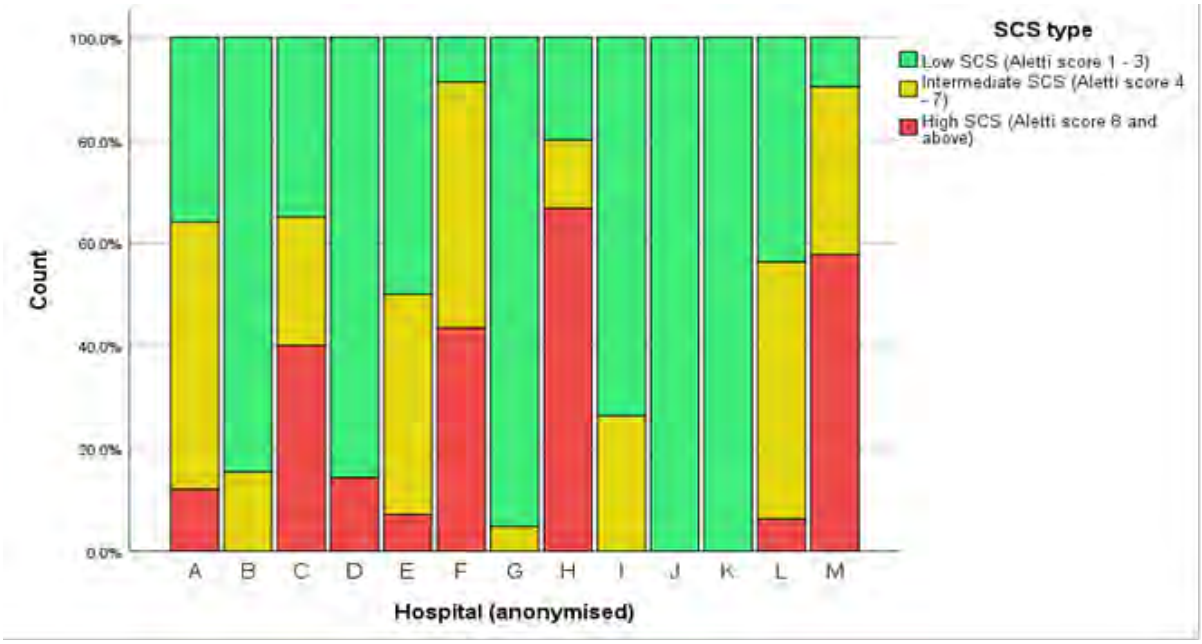



**Figure 40: Variation in surgical complexity scores by institution types**

## Discussion:

This is the first international, multicentre, prospective observational study aiming to measure QoL in patients undergoing surgical intervention for advanced ovarian cancer. Post-operative morbidities and survival outcomes are also considered. The high-quality data due to its completeness, accuracy, reliability and excellent PRO data completion rate collected through this research is able to describe the details of surgical intervention, its outcome and variations in practice at different centres.

The main results show that significant variation exists in utilisation of surgical procedures across centres in the UK. Case selection for surgery by different centres is evident as there is a significant variation in preoperative disease load. Whilst, there is an overlap between the PCI in low SCS and intermediate SCS group, the PCI reported in high SCS group was significantly higher than the other

two groups. The majority of patients who had more than 1 cm residual disease after surgery belonged to the low SCS group where upper abdominal disease was present. A higher proportion of patients had grade 3, 4 or 5 post-operative morbidities in high SCS group (25%) compared to low (9%) and intermediate (13%) SCS group of patients; the relative numbers of patients affected was low. The median time from surgery to chemotherapy was 31 days for low and intermediate SCS groups and 39 days for patients in high SCS group.

The data show that patients who had relatively lower PCI at surgery, but had maximal efforts for cytoreduction (intermediate SCS group) had better PFS and OS compared to low SCS (lower PCI but higher proportion of patients with residual disease) and high SCS (high pre-operative disease load) group of patients. Residual disease at the end of surgery in all groups strongly influenced survival outcomes.

The analysis of EORTC QLQ-C30 data in SOCQER-2 cohort shows that the quality of life of patients undergoing high complexity surgery is not worse when compared to those having low or intermediate complexity surgery, despite a higher disease load at the start of surgery. Within domains of functional QoL, patients with higher complexity surgery have reported deterioration in their QoL at 6 weeks to 6 months post-surgery in their physical function, role function and emotional function. However, it has improved in parallel with other groups thereafter and reached to a level of no difference by 12 months.

Similar findings were reported in prospective longitudinal feasibility SOCQER-1 study, where patients with higher complexity surgeries reached their baseline score by 6 to 9 months (Soo Hoo et al., 2015). Angioli et al described QoL

between the groups having pelvic surgeries against upper abdominal surgeries in the same EORTC domains, but the quality of methodology and data analysis does not provide confidence. However, it did not show a difference in QoL in any functional or symptom scale in both groups (Angioli et al., 2013).

The global QoL in high SCS group remained comparable to low and intermediate SCS group up to 18 months, but it showed some deterioration thereafter, as also with social function. By this time-point, due to the progression of disease, more than half of the patients did not participate in PROM data. It may be the result of attrition bias; however, the possibility and fear of impending progression resulting in a bias in response rates cannot be ruled out. Overall, it appears that the disease burden plays an important role. Patients with high SCS have similar QoL to those with lower disease burden and that may represent as higher complexity of surgery negates the effect of higher disease burden by reducing their preoperative disease load and leading to no clinically important difference in QoL. Analysis of intra-operative and post-operative morbidity did not show any deleterious effect on health in higher complexity surgery group either, except for Clavien-Dindo grade 4 morbidities in high SCS group (7 events in high SCS group vs 1 event in intermediate SCS group) which could be considered an acceptable risk for such type of surgery. Given the disease burden, post-operative morbidities associated with higher complexity surgeries are much lower in our cohort (14.2%) than in retrospective studies (Chi et al., 2010, Kommoss et al., 2010, Rafii et al., 2012). Moreover, most of these complications are Clavien-Dindo Grade 3 and only 8 events (3.4%) of grade 4 morbidity were reported. The exact reasons for this low morbidity rate are not known but possible reasons could include; high NACT

utilisation, a lower proportion of patients receiving high complexity surgeries (26%), or missing post-operative complication data due to patient's geographical locations away from reporting centres. The post-operative mortality in our cohort was 1.2%, as indeed reported in previous studies (Aletti et al., 2006, Chi et al., 2010, Kommoss et al., 2010, Rafii et al., 2012).

Similarly, patients with lower PCI, undergoing intermediate complexity surgery and achieving no residual disease status demonstrated best progression free and overall survival. For progression free survival, ACCI >2 and upper abdominal disease remained independent predictors, whereas low SCS, ACCI >2, pre-operative albumin level <35, and PCI > 15 were independent predictors for overall survival. There were no differences in the PFS and OS whether patients received PDS or NACT or by their location (India Vs UK). Survival outcomes were worse if there were any residual disease after any type of surgery.

**Strengths:** This is a well-designed study and well conducted study with clear goals at the outset and with confounders addressed at the outset. Centres with variations in case selection and use of different types of surgical complexity participated in the study, providing different levels of disease load and different types of surgical intervention, allowing us to understand variation in patient selection and types of procedures performed. The prospective identification of potential candidates for the study and their strict follow-up supported by appropriate staff and patient participation enhances the quality of this study as the loss to follow-up rate has been one of the most criticised and problem areas for such types of studies. All clinical and surgical data were checked and ensured relevant before Aletti scoring by one surgeon and checking by another surgeon

experienced in ovarian cancer surgery. Valid tools were used to analyse surgical and QoL data. There were minimal missing data (>99% data fields complete) for clinical and surgical information, and >85% data were available for patient reported outcomes. We also produced a validated Bengali translation for EORTC QLQ-OV28 and CR29 in collaboration with EORTC team at Belgium (Appendix SQR6), so that, our non-English speaking patients at Kolkata were able to understand and report PROMs appropriately.

**Limitations:** The QoL dataset produced was large and due to multiple testing, it may be possible, that we have found some statistically significant differences by chance. All centres were allowed recruitment for only one year, and therefore, with not all patients participating into the study, a true reflection of centre patient population and practice cannot be ascertained. Due to some missing data, complete case analysis was limited to about 60% of population for general linear repeated measures. Further repeated measures analysis after imputing the missing data is planned, but it is beyond the scope of this thesis.

Confounding factors may exist in this particular study at each level as differences could be present in patient's characteristics, disease's nature, operating surgeon's experience, oncological treatment and patient's response to treatment. A direct comparison between the SCS groups may seem inappropriate as there are known and may be unknown confounders present, however, directly reporting experience of high complexity surgery and QoL following such treatment is still of paramount importance for patients, clinicians and policy makers.

**Interpretation of findings:** Policies to undertake types and timing of surgical intervention varies across different centres leading to variance in case selection.

Complexity of debulking surgery varies according to disease load, but it is also hugely dependent on the surgeon's belief, training and experience. As these are complex variables to control but exist widely, the outcome of such surgical intervention would differ and would potentially affect survival outcomes. Although it is evident in many retrospective studies that higher complexity surgery achieves higher successful debulking, as in our cohort in SOCQER-2, it is important to understand morbidities and QoL outcomes associated with this. In our cohort, although the associated morbidities are higher in high SCS group than lower complexity surgery, it is still not leading to any harmful effect on their quality of life. Most of the patients demonstrated equivalent QoL across different groups of variables by 6 months post-surgery. Some domains of QoL such as physical function and role function may take up to 6 to 12 months to improve in high SCS group of patents; statistically and clinically important improvements are demonstrated across various domains of QoL by all patients receiving surgical intervention within the groups. Disease related symptoms show significant improvement in most domains, however, side effects of chemotherapy such as peripheral neuropathy, body image and fatigue can be present for longer durations after treatment.

**Self-evaluation and lost opportunities:** This study expanded my understanding of research methodology, critical and analytical thinking and development of knowledge of applied statistics. The work load ranged from reviewing current knowledge, performing a meta-analysis, team working and timely communication of all key members to ensure correct data is reported on time. The important challenges encountered during the study were understanding the validity of data

and the timely follow-up of the participants. An understanding of the validity of the data was mainly related to the correlation between the disease distribution and surgical procedures performed for each patient and a meticulous approach by qualified personnel was needed to achieve this. The challenge of appropriate follow-up was accomplished by having a sincere team work between the research centre and all participating sites.

As the research remained focussed on the outcome of those patients who underwent successful surgery, an opportunity to investigate QoL of those patients with abandoned surgery due to a high volume of disease load and only received chemotherapy was missed. Similarly, an opportunity to understand QoL of those patients who relapsed during the study duration was also not undertaken. I believe, that these results would not be free of biases and cannot be compared to other groups, but understanding their QoL could have been an additional experience. An addition to these parameters along with psychological QoL would be valued in future research.

## Conclusions:

Morbidities associated to higher complexity surgeries are not excessive, given the types of procedures performed in our study cohort, and patients tolerate the procedures well. Little deleterious effect on patient's quality of life has been observed in higher complexity surgeries compared to lower complexity surgeries. Therefore, for clinical practice, the data provides confidence in the use of extensive surgical procedures in the treatment of advanced ovarian cancer without having a significant effect in global QoL of patients, however, the limitations of functional QoL, especially physical ability for up to 6 months post-surgery needs to

be discussed along with survival gain while sharing information with the patients. The study indicates that patient's co-morbidity and disease burden are important predictors of survival and any decision for treatment should address these factors. One of the most important highlight of this study is the demonstration of existence of wide variation in patient selection and surgical intervention across centres in the UK.

# Appendix SQR1: Baseline CRF

**Please complete the Baseline CRF in full and return by post to the University of Birmingham**
**If you have any questions please contact Dr Joanna Long**

1) Record ID _____

2) Patient's First name _____

3) Patient's surname _____

4) Patient's Date of Birth _____

5) NHS number _____

5) Local patient identifier _____
The identifier used on the patient administration system of the treatment provider

7) Identifying hospital _____
What was the name of the hospital at which the patient was identified?

8) Ethnic group (please tick)

| | | | |
|---|---|---|---|
| White British | ☐ | Asian or Asian British | ☐ |
| White Irish | ☐ | Any other Asian background | ☐ |
| White Any other White background | ☐ | Black or Black British Caribbean | ☐ |
| Mixed White and Black Caribbean | ☐ | Black or Black British African | ☐ |
| Mixed White and Black African | ☐ | Black or Black British | ☐ |
| Mixed White and Asian | ☐ | Any other Black background | ☐ |
| Mixed Any other mixed background | ☐ | Chinese | ☐ |
| Asian or Asian British Indian | ☐ | Any other ethnic group | ☐ |
| Asian or Asian British Pakistani | ☐ | Not stated | ☐ |
| Asian or Asian British Bangladeshi | ☐ | Missing/Not given | ☐ |

9) Patient height (in centimetres) _____cm

10) Patient weight (in kg) _____kg

**Research use only:**

BMI:

11) Previous abdominal surgery (please tick any that apply)
Has the patient previously had either / both of these procedures?

Hysterectomy☐ Oopherectomy ☐ None ☐ Other☐ (please specify)
_____

12) Baseline CA125 date (at diagnosis) (dd/mm/yy) _ _ / _ _ / _ _

13) Baseline CA125 result (U/ml) (at diagnosis) _____

14) Serum albumin date (most recent) (dd/mm/yy) _ _ / _ _ / _ _

15) Serum albumin result (g/dL) (most recent) _____

16) Hb date (most recent) (dd/mm/yy) _ _ / _ _ / _ _

17) Hb result (most recent) _____

18) Baseline treatment plan (please tick):

| | |
|---|---|
| Primary debulking | ☐ |
| Interval debulking | ☐ |

**If 'Primary debulking' is ticked in question 15, you have now finished the Baseline CRF:**

**Date _ _ / _ _ / _ _ Completed by _____**

**If you ticked 'Interval debulking' or 'Neoadjuvant chemotherapy, with intended interval debulking' please continue with <u>questions 18-21</u>**

19) If NACT or interval debulking, how was diagnosis made:

| | |
|---|---|
| Laparotomy / debulking | ☐ |
| Laparoscopic biopsy | ☐ |
| Ascities cytology | ☐ |
| Imaging guided biopsy | ☐ |
| Pleural effusion cytology | ☐ |

20) Reason(s) not to start primary debulking (please tick all that applies):

| | |
|---|---|
| Tumour load | ☐ |
| Poor performance status | ☐ |
| Stage 4 disease | ☐ |
| Pleural effusion | ☐ |
| Omental disease >5cm | ☐ |
| Massive ascites | ☐ |
| Suspected bowel involvement | ☐ |
| Upper abdo. disease on imaging | ☐ |
| Enlarged paraaortic lymph nodes | ☐ |
| Other (please specify): _____ | ☐ |

21) Which Neoadjuvant chemotherapy used (please tick all that applies):

| | |
|---|---|
| Carboplatin alone | ☐ |
| 3 weekly carboplatin and taxol | ☐ |
| 3 weekly carboplatin and weekly taxol | ☐ |
| With Bevazicumab | ☐ |
| Other (please specify): _____ | ☐ |

**Baseline CRF is now completed. Date _ _ / _ _ / _ _ Completed by _____**

# Appendix SQR2: Surgical CRF

**Please complete the Surgical CRF in full and return by post to the University of Birmingham**
**If you have any questions please contact Dr Joanna Long**

1) Record ID _____

2) Patient First name _____

3) Patient Last name _____

4) NHS number _____

5) Provider: Please tick the provider Trust in which the surgery was performed:

| | | | |
|---|---|---|---|
| Sandwell and West Birmingham NHS Trust | ☐ | Barts and the London NHS Trust | ☐ |
| Imperial College Healthcare NHS Trust | ☐ | Southend University Hospital NHS Trust | ☐ |
| Lancashire Teaching Hospitals NHS FT | ☐ | Norfolk and Norwich University Hospitals NHS FT | ☐ |
| Sheffield Teaching Hospitals | ☐ | Central Manchester University Hospitals NHS FT | ☐ |
| Ysbyty Gwynedd - Bangor | ☐ | Leeds Teaching Hospitals NHS Trust | ☐ |
| Gateshead Health NHS FT | ☐ | Taunton and Somerset NHS FT | ☐ |
| St George's Healthcare NHS Trust | ☐ | Royal Marsden Hospital NHS FT | ☐ |

6) Date of Surgery (dd/mm/yy): ___/___/___

7) Principal surgeon (please circle):

Consultant Sub-speciality trainee Other (please specify)_____

8) Assistant surgeon (please circle):

Consultant Sub-speciality trainee Other (please specify)_____

9) Other operating surgeon specialists (circle all which apply):

Colorectal surgeon Upper GI surgeon Urology surgeon

Other (please specify)_____

10) Comorbidity (Tick all that are present):

| | | | |
|---|---|---|---|
| Myocardial infarct (+1) | ☐ | Diabetes (without complications) (+1) | ☐ |
| Congestive heart failure (+1) | ☐ | Diabetes with end organ damage (+2) | ☐ |
| Peripheral vascular disease (+1) | ☐ | Hemiplegia (+2) | ☐ |
| Cerebrovascular disease (except hemiplegia) (+1) | ☐ | Moderate or severe renal disease (+2) | ☐ |
| Dementia (+1) | ☐ | Leukemia (+2) | ☐ |
| Chronic pulmonary disease (+1) | ☐ | Lymphoma, Multiple myeloma (+2) | ☐ |
| Connective tissue disease (+1) | ☐ | Moderate or severe liver disease (+3) | ☐ |
| Ulcer disease (+1) | ☐ | AIDS (+6) | ☐ |

| | | | |
|---|---|---|---|
| Mild liver disease (+1) | ☐ | None | ☐ |

11) Age (please tick):

| | |
|---|---|
| Under 50 (0) | ☐ |
| 50-59 (+1) | ☐ |
| 60-69 (+2) | ☐ |
| 70-79 (+3) | ☐ |
| 80-89 (+4) | ☐ |
| 90-99 (+5) | ☐ |

**Research use only:**

Total score Q10+11:

12) ECOG Performance status (please tick):

| | | |
|---|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction. | ☐ |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light sedentary nature, e.g. light house work. | ☐ |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. | ☐ |
| 3 | Capable of only limited self care, Confined to bed or chair more than 50% of waking hours. | ☐ |
| 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair. | ☐ |

13) BMI (Body-mass index) _____

14) What was the timing of surgery? (please circle):

Primary Debulking  Interval Debulking (post NACT)

**If you selected 'Primary Debulking' please skip to <u>question 17</u>**

15) If post NACT debulking, how many chemotherapy cycles were there? _____

16) If post NACT debulking, what was chemotherapy response prior to surgery? (please circle)

Good  Partial  Stable disease  Other (please specify)_____

17) What was the last CA125 result prior to surgery (U/ml) _____

18) Peritoneal Cancer Index: Abdominal region(s) (please enter lesion size score 0, 1, 2 ,3 only for each quadrant). See diagram for reference in Appendix A:

| | | **BEFORE SURGERY** | **AFTER SURGERY** |
|---|---|---|---|
| | Region | Lesion size score (0/1/2/3)<br>0 – No lesion seen<br>1 – Lesion size up to 0.5 cm<br>2 – LS up to 5 cm<br>3 – LS more than 5 cm | Lesion size score (0/1/2/3)<br>0 – No lesion seen<br>1 – Lesion size up to 0.5 cm<br>2 – LS up to 5 cm<br>3 – LS more than 5 cm |
| 0 | Central | | |
| 1 | Right upper | | |
| 2 | Epigastrium | | |
| 3 | Left upper | | |
| 4 | Left flank | | |
| 5 | Left lower | | |
| 6 | Pelvis | | |
| 7 | Right lower | | |
| 8 | Right flank | | |
| 9 | Upper jejunum | | |
| 10 | Lower jejunum | | |
| 11 | Upper ileum | | |
| 12 | Lower ileum | | |
| | **Research use only: PCI Score** | | |

19) Please provide details of hysterectomy (please tick):

| | | | |
|---|---|---|---|
| Total hysterectomy | ☐ | Hysterectomy not technically possible | ☐ |
| Sub-total hysterectomy | ☐ | Other (please specify):<br>_____ | ☐ |
| Hysterectomy previously performed | ☐ | | |

20) Provide details of salpingo-oophrectomy (please tick):

| | | | |
|---|---|---|---|
| Unilateral | ☐ | Not technically possible | ☐ |
| Bilateral | ☐ | Not performed | ☐ |
| Previously performed, unilateral | ☐ | Other (please specify):<br>_____ | ☐ |
| Previously performed, bilateral | ☐ | | |

21) Indicate which procedures were performed on lymph nodes (please tick):

| | | | |
|---|---|---|---|
| Sampling of pelvic LN | ☐ | Systemic lymphadenectomy (para-aortic) | ☐ |
| Systemic lymphadenectomy (pelvic) | ☐ | Removal of bulky para-aortic LN | ☐ |
| Removal of bulky pelvic LN | ☐ | Resection of supradiaphragmatic LN | ☐ |
| Sampling of para-aortic LN | ☐ | Not performed | ☐ |

22) Provide details of para-aortic lymph node surgery (please tick):

| | |
|---|---|
| Not performed | ☐ |
| Sampling only | ☐ |
| Systemic lymphadenectomy | ☐ |
| Removal of bulky para aortic lymph nodes only | ☐ |

23) Were supradiaphragmatic lymph nodes resected? (please circle):

Yes No

24) Provide details of omentectomy (please tick):

| | | | |
|---|---|---|---|
| Not performed | ☐ | Partial / infracolic omentectomy | ☐ |
| Complete / supra and infracolic omentectomy | ☐ | Other (please specify): _____ | ☐ |

25) Provide details of stoma formation (please tick):

| | | | |
|---|---|---|---|
| Not performed | ☐ | Ileostomy | ☐ |
| Colostomy | ☐ | Other (please specify): _____ | ☐ |

26) Indicate which procedures were performed on the bowel (please tick any which apply):

| | | | |
|---|---|---|---|
| Small bowel resection | ☐ | Anastomosis: Small bowel | ☐ |
| Large bowel resection | ☐ | Recto-sigmoidectomyIn | ☐ |
| Anastomosis: Large bowel | ☐ | Not performed | ☐ |

27) Indicate which urological procedures were performed (please tick any which apply):

| | |
|---|---|
| Ureteric resection preformed | ☐ |
| Bladder wall resection performed | ☐ |
| Ureteric reimplantation performed | ☐ |
| Not performed | ☐ |

28) Indicate which procedures were performed on the peritoneum (please tick):

| | | | |
|---|---|---|---|
| Pelvic peritonectomy | ☐ | Parietal peritonectomy | ☐ |
| Not performed | ☐ | | |

29) Indicate which procedures were performed on the liver (please tick any which apply):

| | | | |
|---|---|---|---|
| Liver capsule resection | ☐ | Partial hepatectomy | ☐ |
| Wedge resection | ☐ | Removal lymph nodes / tumour porta hepatis | ☐ |
| Not performed | ☐ | | |

30) Indicate which procedures were performed on other anatomical areas (please tick any which apply):

| | | | |
|---|---|---|---|
| Full thickness diaphragmatic resection | ☐ | Partial gastrectomy | ☐ |
| Removal of isolated deposit on diaphragm | ☐ | Splenectomy | ☐ |
| Diaphragmatic peritonectomy without opening of the chest | ☐ | Resection of lesser sac / celiac trunk | ☐ |
| Resection of tail of pancreas | ☐ | Any other resection (please specify): _____ | ☐ |
| Cholesystectomy | ☐ | No further procedures performed | ☐ |

31) Categorise the debulking outcome (please tick):

| | |
|---|---|
| No visible disease | ☐ |
| Less than 1cm residual disease | ☐ |
| More than 1cm residual disease | ☐ |
| Inoperable (open/close laparotomy) | ☐ |

**If you ticked 'Debulked to <=1cm residual disease' OR 'Debulked to >1cm residual disease' please go to question 32**

**If you ticked 'Debulked to no visible disease' or 'Inoperable biopsies' please go to question 33**

32) Where residual disease was known to be left in situ, please state the reason (please tick):

| | | | |
|---|---|---|---|
| Technical difficulties in resection | ☐ | Lack of theatre time | ☐ |
| Patient unfit to undergo procedure | ☐ | Surgical ethos | ☐ |
| Surgery performed with palliative intent | ☐ | Other (please specify): _____ | ☐ |

33) Patient in another ovarian cancer treatment study? Yes ☐ / No ☐

34) Estimate the blood loss in the surgical episode (please tick):

| | | | |
|---|---|---|---|
| < 500 ml | ☐ | >3 - 4 litres | ☐ |
| 500 ml - 1 litre | ☐ | >4 – 5 litres | ☐ |
| >1 - 2 litres | ☐ | > 5 litres | ☐ |
| >2 – 3 litres | ☐ | | |

35) Approximate duration of operation (knife to skin closure):

| | | | |
|---|---|---|---|
| up to 1 hour | ☐ | >4 – 5 hours | ☐ |
| >1 - 2 hours | ☐ | >5 – 6 hours | ☐ |
| >2 – 3 hours | ☐ | >6 – 7 hours | ☐ |
| >3 – 4 hours | ☐ | >7 hours | ☐ |

36) Intra-operative complications - tick all that apply:

| | |
|---|---|
| None | ☐ |
| Anaesthetic complications | ☐ |
| Cardiac | ☐ |
| Respiratory | ☐ |
| Allergic reactions | ☐ |
| Vascular injury | ☐ |
| GI tract injury – Stomach | ☐ |
| GI tract injury - Small bowel | ☐ |
| GI tract injury - Large bowel | ☐ |
| Bladder injury | ☐ |
| Ureteric injury | ☐ |
| Death | ☐ |
| Other intra-operative complications (please specify)/ Provide brief details of the complication: _____ | ☐ |

**If 'death' ticked as intra operative complication, please answer questions 36-39**

**If not, Surgical CRF is now completed. Date _ _ / _ _ / _ _ Completed by _____**

37) Primary cause of death on death certificate. (ICD10 4 digit or full text):

_____

_____

38) Secondary cause of death on death certificate. (ICD10 4 digit or full text):

_____

_____

39) Secondary cause of death on death certificate. (ICD10 4 digit or full text):

_____

_____

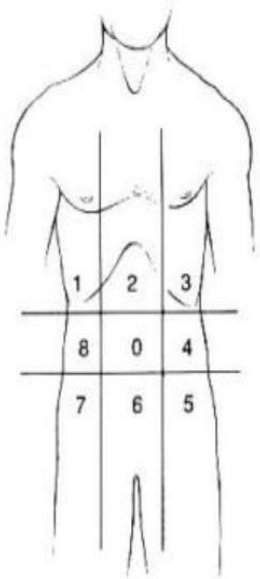
40) Other significant conditions contributing to death but not related to the disease or condition causing it (ICD10 4 digit or full text):

_____

_____

**Surgical CRF is now completed. Date _ _ / _ _ / _ _ Completed by _____**

**PCI Diagram**




**Regions** | **Lesion Size**

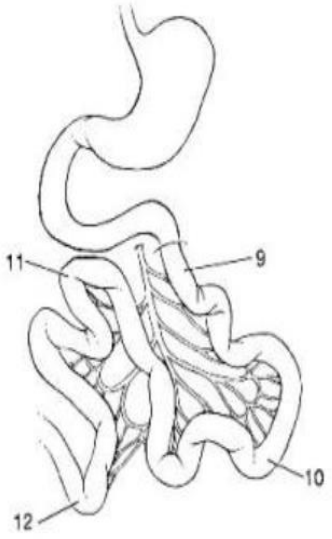
0 Central ____
1 Right Upper ____
2 Epigastrium ____
3 Left Upper ____
4 Left Flank ____
5 Left Lower ____
6 Pelvis ____
7 Right Lower ____
8 Right Flank ____

9 Upper Jejunum ____
10 Lower Jejunum ____
11 Upper Ileum ____
12 Lower Ileum ____

**PCI** ☐

**Lesion Size Score**

LS 0 No tumor seen
LS 1 Tumor up to 0.5 cm
LS 2 Tumor up to 5.0 cm
LS 3 Tumor > 5.0 cm or confluence



# Appendix SQR3: Post-operative CRF

**Please complete the Post-Operative CRF in full and return by post to the University of Birmingham. If you have any questions please contact Dr Joanna Long**

1) Record ID _____

2) Patient First name _____

3) Patient Last name _____

4) NHS number _____

Surgery in Ovarian Cancer Quality of Life Evaluation Research

5) Did the patient require an episode of care in an ITU after surgery? (please circle):

Yes No

5a) If YES, for how many whole days was the patient in the unit? _____days

6) Were there any post-operative complications? Please **tick all that apply**. If none then leave blank:

| | | | |
|---|---|---|---|
| No post-operative complications | ☐ | Sepsis – with single organ failure | ☐ |
| Primary haemorrhage requiring blood transfusion | ☐ | Sepsis – with multiple organ failure | ☐ |
| Primary haemorrhage requiring return to theatre within 24 hours | ☐ | Anastomotic leak – conservative/ surgical management | ☐ |
| Secondary haemorrhage requiring blood transfusion | ☐ | Ileus – conservative management including NG tube | ☐ |
| Secondary haemorrhage requiring return to theatre within 24 hours | ☐ | Bowel obstruction – conservative/ surgical management | ☐ |
| Abscess/haematoma – requiring drainage without GA | ☐ | Bladder – retention/ dysfunction | ☐ |
| Abscess/haematoma – requiring drainage with GA | ☐ | Ureteric obstruction – radiological/ surgical management | ☐ |
| Wound breakdown requiring conservative management | ☐ | DVT – confirmed and required therapeutic anticoagulation | ☐ |
| Wound breakdown requiring surgical management | ☐ | PE – confirmed and required therapeutic anticoagulation | ☐ |
| Lymphocyst / Lymphoedema requiring radiological drainage | ☐ | Cardiac – arrhythmias/ infarction/ failure | ☐ |
| Lymphocyst / Lymphoedema requiring surgical drainage | ☐ | Respiratory – pneumonia/ failure | ☐ |
| Sepsis (Please tick appropriate section below under sepsis) | ☐ | Neurological – brain haemorrhage/ ischaemic stroke | ☐ |
| Sepsis – requiring systemic antibiotics | ☐ | Fistula – conservative/ surgical management | ☐ |
| Sepsis – requiring ITU admission | ☐ | Other (please specify) _____ | |

7) Please give us any further information regarding post operative complications, if you would like:

_____

_____

8) What was the date of discharge from the hospital in which the surgical episode took place (dd/mm/yy): _ _ / _ _ / _ _

9) Was there an unplanned (emergency) admission to hospital within 6 weeks of discharge from the spell in which the surgical episode occurred?

Yes No

10) If YES, briefly describe the reason(s) for unplanned readmission (free text description or ICD 10 code):

11) Final histological diagnosis. Please **tick one:**

| | | | |
|---|---|---|---|
| Serous – low grade | ☐ | Mucinous | ☐ |
| Serous – high grade | ☐ | Undifferentiated / unclassifiable | ☐ |
| Endometroid | ☐ | Other (please specify): _____ | ☐ |
| Clear cell | ☐ | | |

12) Final FIGO stage (please tick):

| | | | |
|---|---|---|---|
| Stage 1A | ☐ | Stage 3A2 | ☐ |
| Stage 1B | ☐ | Stage 3B | ☐ |
| Stage 1C | ☐ | Stage 3C | ☐ |
| Stage 2A | ☐ | Stage 4A | ☐ |
| Stage 2B | ☐ | Stage 4B | ☐ |
| Stage 3A1 | ☐ | Not recorded/available | ☐ |

13) What chemotherapy did the patient receive after surgery (please tick):

| | | | |
|---|---|---|---|
| Caboplatin alone | ☐ | Three weekly caboplatin and weekly taxol | ☐ |
| Taxol alone | ☐ | With Bevazicumab | ☐ |
| Three weekly carboplatin and taxol | ☐ | Other (please specifiy) _____ | ☐ |

14) What date did the patient begin post-operative chemotherapy (dd/mm/yy):
_ _ / _ _ / _ _

**Post-operative CRF is now completed. Date _ _ / _ _ / _ _ Completed by _____**

# Appendix SQR4: Outcome CRF

**Please complete the 18 month outcome CRF in full and return by post to the University of Birmingham. If you have any questions please contact Dr Joanna Long**

1) Record ID _____

2) Patient First name _____

3) Patient Last name _____

4) NHS number _____

Surgery in Ovarian Cancer Quality of Life Evaluation Research

5) What is patient status at 18 months post discharge? (please tick):

| | | |
|---|---|---|
| Alive | ☐ | |
| Deceased | ☐ | |
| Lost to follow-up | ☐ | Reason for loss to follow up _____ |
| Withdrawn | ☐ | Reason for withdrawl _____ |
| Did not have surgery | ☐ | Reason for not having surgery _____ |

**If patient has DECEASED please go to question 10 (next page)**

6) Has patient progressed at any point up to 18 months post discharge (please circle):

Yes No Not known

**If YES, please complete questions 7-9 ONLY**

**If NO, 18 month outcome CRF is now completed. Date _ _ / _ _ / _ _ Completed by _____**

7) What was the date of disease progression as confirmed by treating clinician (dd/mm/yy):
_ _ / _ _ / _ _

8) What treatment options were planned once progression was confirmed (please tick):

| | |
|---|---|
| Chemotherapy | ☐ |
| Palliation | ☐ |
| Surgery | ☐ |
| Other (please specify): _____ | ☐ |

9) Which diagnostic methods were used to ascertain disease progression (please tick):

| | |
|---|---|
| Radiological | ☐ |
| Clinical | ☐ |
| CA125 elevation | ☐ |

10) Date of death (if known) (dd/mm/yy): _ _ / _ _ / _ _

11) Primary cause of death on death certificate. (ICD10 4 digit or full text):

_____

_____

12) Secondary cause of death on death certificate. (ICD10 4 digit or full text):

_____

_____

13) Secondary cause of death on death certificate. (ICD10 4 digit or full text):

_____

_____

14) Other significant conditions contributing to death but not related to the disease or condition causing it (ICD10 4 digit or full text):

_____

_____

**18 month outcome CRF is now completed. Date _ _ / _ _ / _ _ Completed by _____**

# Appendix SQR5: AKI CRF

**Please complete the following case report form and return by post to the University of Birmingham. The address to post if provided overleaf. If you require any further assistance, please contact Dr Satyam Kumar at**

1) Study ID _____

2) NHS number _____

| | | | | |
|---|---|---|---|---|
| 1 | **Is there a history of diabetes?** | No | ☐ | Please go to question 2 |
| | | Yes | ☐ | Please answer below |
| | 1a. Type of diabetes | Type 1 | ☐ | |
| | | Type 2 | ☐ | |
| | 1b. Type of treatment received | | | |
| | Diet control | | ☐ | |
| | Oral hypoglycaemics | | ☐ | |
| | Insulin | | ☐ | |
| | Others | | ☐ | |
| | None | | ☐ | ⇨ |
| 2 | **Is there a history of Hypertension?** | No | ☐ | Please go to question 3 |
| | | Yes | ☐ | Please answer below |
| | 2a. Type of treatment received | | | |
| | ACE inhibitor | | ☐ | |
| | Angiotensin receptor antagonist | | ☐ | |
| | Others (please specify) | | ☐ | ⇨ |
| | None | | ☐ | |
| 3 | **Did the patient receive blood products during the surgical intervention?** ( Please tick all that apply) | | | |
| | No | | ☐ | Please go to question 4 |
| | Pre-operative | | ☐ | |
| | Intra-operative | | ☐ | |
| | Post-operative | | ☐ | |
| 4 | **Did this patient receive post- operative NSAID?** | No | ☐ | |
| | | Yes | ☐ | |

| 5 | **Please complete the investigation chart below** |
|---|---|

| | At diagnosis before starting any treatment | Pre-operative | Post-op D1-D2 (most deranged value) | Post-op D3-D5 (most deranged value) | At discharge from hospital after surgery | 4-6wks post –op / pre-chemo Rx | 3 month post-op | 6 month post-op |
|---|---|---|---|---|---|---|---|---|
| **Serum creatinine (µmol/L)** | | | | | | | | |
| **eGFR (ml/ml/1.73m$^2$)** | | | | | | | | |
| **Hb (g/L)** | | | | | | | | |

| | | | |
|---|---|---|---|
| 6 | **Steps taken to manage a diagnosed acute kidney injury** ( please tick all that apply) | | |
| | Fluid challenge | ☐ | |
| | Discontinuation of NSAIDs | ☐ | |
| | Discontinuation of ACE inhibitors or angiotensin receptor antagonists | ☐ | |
| | Referral to renal medicine | ☐ | |
| | HDU/ITU care for management of renal failure | ☐ | |
| | Others ( please specify) | ☐ | ⇨ |
| | Not applicable | ☐ | |
| 7 | **Type of renal replacement therapy received** | | |
| | None | ☐ | |
| | Haemodialysis | ☐ | |
| | Haemofiltration | ☐ | |
| | Plasmaphersis | ☐ | |
| | Others (please specify) | ☐ | ⇨ |

**Date _ _ / _ _ / _ _ Completed by _____**

**Notes :**

1. NSAIDs – Ibuprofen, Diclofenac, Aspirin, etc;

2. ACE inhibitors- Rami***pril***, Capto***pril***, Enala***pril***, etc; Angiotensin receptor antagonists- lo***sartan*** etc. (please refer to BNF if in doubt or specify in the space provided next to the question).

**3. Please return the completed forms FAO**

Dr Satyam Kumar
Clinical research fellow
[redacted]
Or send it by secured email to [redacted]

## Appendix SQR6: EORTC certificate


Dagmara Kuliś
Translation Team Leader
Quality of Life Department

Brussels, 8th February 2017

**CONFIRMATION**

Hereby we confirm that Dr Satyam Kumar translated and linguistically validated the Ovarian Module (QLQ-OV28) and the Colorectal Module (QLQ-CR29) in Bengali. The process was coordinated by the EORTC and followed the EORTC Translation Procedure. We also acknowledge the support of Mrs Sundar / Dr Cummins - University of Birmingham and Dr Mukhopadhyay and S. Mondal from Kolkata.

Signed by:

*Dagmara Kuliś*
Translation Team Leader, EORTC Headquarters, Brussels
for EORTC Quality of Life Group

# Appendix SQR7: QLQ-C30

## EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 6. Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. Have you had pain? | 1 | 2 | 3 | 4 |
| 10. Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. Have you vomited? | 1 | 2 | 3 | 4 |
| 16. Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

# Scoring the EORTC QLQ-C30 version 3.0

**Table 1: Scoring the QLQ-C30 version 3.0**

| | Scale | Number of items | Item range* | Version 3.0 Item numbers | Function scales |
|---|---|---|---|---|---|
| **Global health status / QoL** | | | | | |
| Global health status/QoL (revised)† | QL2 | 2 | 6 | 29, 30 | |
| **Functional scales** | | | | | |
| Physical functioning (revised)† | PF2 | 5 | 3 | 1 to 5 | F |
| Role functioning (revised)† | RF2 | 2 | 3 | 6, 7 | F |
| Emotional functioning | EF | 4 | 3 | 21 to 24 | F |
| Cognitive functioning | CF | 2 | 3 | 20, 25 | F |
| Social functioning | SF | 2 | 3 | 26, 27 | F |
| **Symptom scales / items** | | | | | |
| Fatigue | FA | 3 | 3 | 10, 12, 18 | |
| Nausea and vomiting | NV | 2 | 3 | 14, 15 | |
| Pain | PA | 2 | 3 | 9, 19 | |
| Dyspnoea | DY | 1 | 3 | 8 | |
| Insomnia | SL | 1 | 3 | 11 | |
| Appetite loss | AP | 1 | 3 | 13 | |
| Constipation | CO | 1 | 3 | 16 | |
| Diarrhoea | DI | 1 | 3 | 17 | |
| Financial difficulties | FI | 1 | 3 | 28 | |

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.
† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$$

Then for **Functional scales**:

$$Score = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$$

and for **Symptom scales / items** and **Global health status / QoL:**

$$Score = \{(RS-1)/range\} \times 100$$

**Examples:**

Emotional functioning

$$RawScore = (Q_{21} + Q_{22} + Q_{23} + Q_{24})/4$$
$$\text{EF } Score = \{1 - (RawScore - 1)/3\} \times 100$$

Fatigue

$$RawScore = (Q_{10} + Q_{12} + Q_{18})/3$$
$$\text{FA } Score = \{(RawScore - 1)/3\} \times 100$$

## Questions comprising different domains of QoL:

1. **Global QoL**
    a. How would you rate your overall health during last week?
    b. How would you rate your overall quality of life during last week?
2. **Functional QoL – Physical function**
    a. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?
    b. Do you have any trouble taking a long walk?
    c. Do you have any trouble taking a short walk outside of the house
    d. Do you need to stay in bed or a chair during the day?
    e. Do you need help with eating, dressing, washing yourself or using the toilet?
3. **Functional QoL – Role function**
    a. Were you limited in doing either your work or other daily activities?
    b. Were you limited in pursuing your hobbies or other leisure time activities?
4. **Functional QoL – Emotional function**
    a. Did you feel tense?
    b. Did you worry?
    c. Did you feel irritable?
    d. Did you feel depressed?
5. **Functional QoL – Cognitive function**
    a. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?
    b. Have you had difficulty remembering things?
6. **Functional QoL – Social function**
    a. Has your physical condition or medical treatment interfered with your family life?
    b. Has your physical condition or medical treatment interfered with your social activities?

# Appendix SQR8: QLQ-OV28

## EORTC QLQ - OV28

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 31. Did you have abdominal pain? | 1 | 2 | 3 | 4 |
| 32. Did you have a bloated feeling in your abdomen / stomach? | 1 | 2 | 3 | 4 |
| 33. Did you have problems with your clothes feeling too tight? | 1 | 2 | 3 | 4 |
| 34. Did you experience change in bowel habit as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 35. Were you troubled by passing wind / gas / flatulence? | 1 | 2 | 3 | 4 |
| 36. Have you felt full up too quickly after beginning to eat? | 1 | 2 | 3 | 4 |
| 37. Have you had indigestion or heartburn? | 1 | 2 | 3 | 4 |
| 38. Have you lost any hair? | 1 | 2 | 3 | 4 |
| 39. Answer this question only if you had any hair loss: Were you upset by the loss of your hair? | 1 | 2 | 3 | 4 |
| 40. Did food and drink taste different from usual? | 1 | 2 | 3 | 4 |
| 41. Have you had tingling hands or feet? | 1 | 2 | 3 | 4 |
| 42. Have you had numbness in your fingers or toes? | 1 | 2 | 3 | 4 |
| 43. Have you felt weak in your arms or legs? | 1 | 2 | 3 | 4 |
| 44. Did you have aches or pains in your muscles or joints? | 1 | 2 | 3 | 4 |
| 45. Did you have problems with hearing? | 1 | 2 | 3 | 4 |
| 46. Did you urinate frequently? | 1 | 2 | 3 | 4 |
| 47. Have you had skin problems (e.g. itchy, dry)? | 1 | 2 | 3 | 4 |
| 48. Did you have hot flushes? | 1 | 2 | 3 | 4 |
| 49. Did you have night sweats? | 1 | 2 | 3 | 4 |

Please go on to next page

| **During the past week:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 50. Have you felt physically less attractive as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 51. Have you been dissatisfied with your body? | 1 | 2 | 3 | 4 |
| 52. How much has your disease been a burden to you? | 1 | 2 | 3 | 4 |
| 53. How much has your treatment been a burden to you? | 1 | 2 | 3 | 4 |
| 54. Were you worried about your future health? | 1 | 2 | 3 | 4 |

| **During the past 4 weeks:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 55. To what extent were you interested in sex? | 1 | 2 | 3 | 4 |
| 56. To what extent were you sexually active? | 1 | 2 | 3 | 4 |
| Answer the following two questions only if you were sexually active: | | | | |
| 57. To what extent was sex enjoyable for you? | 1 | 2 | 3 | 4 |
| 58. Did you have a dry vagina during sexual activity? | 1 | 2 | 3 | 4 |

## Appendix SQR9: Principles of scoring - EORTC scoring manual v3.

QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning; a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems. The principle for scoring these scales is the same in all cases.

Steps:

1. Estimate the average of the items that contribute to the scale; this is the raw score.

2. Use a linear transformation to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

For all scales, the Raw Score, RS, is the mean of the component items:

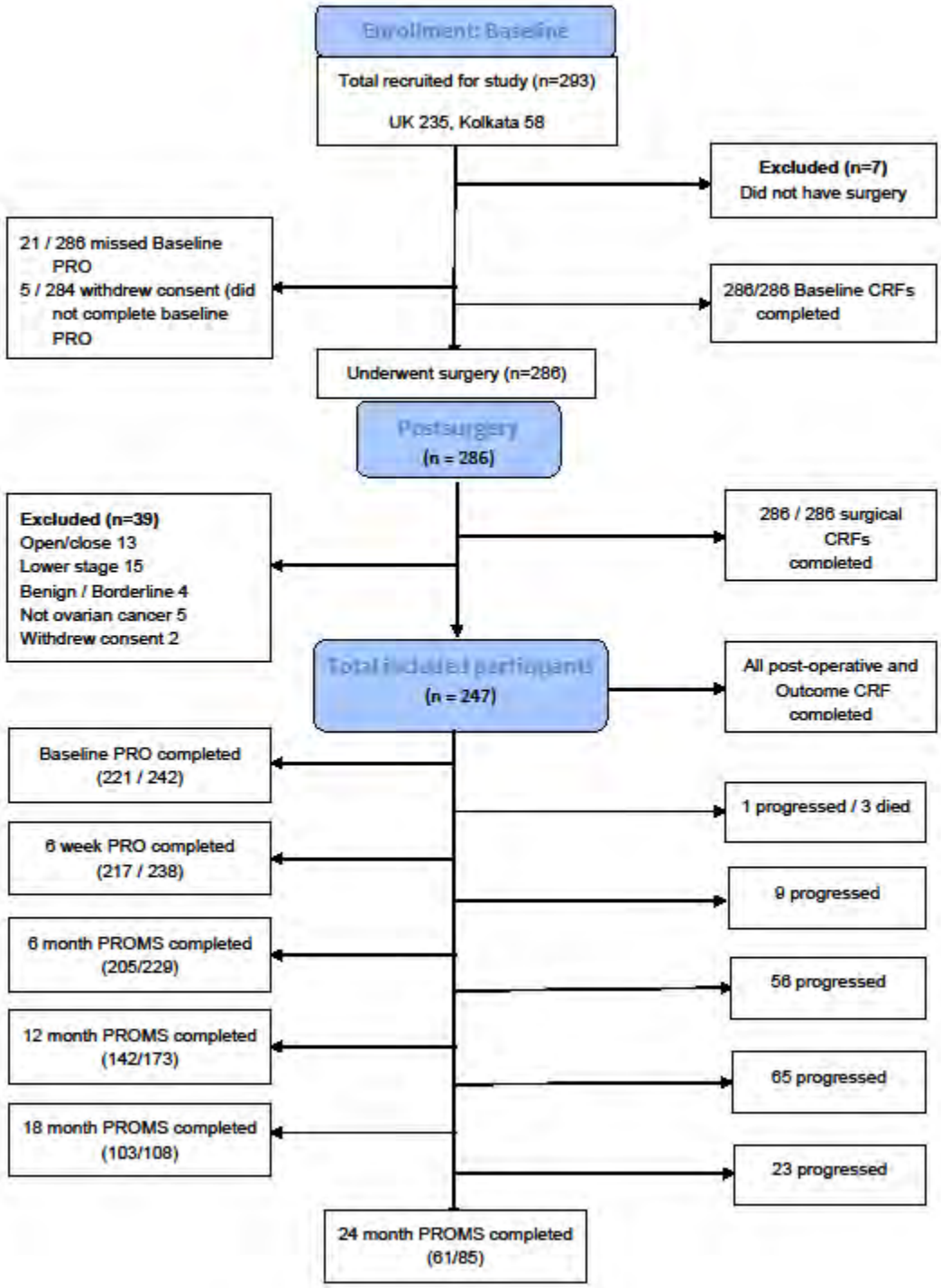
Raw Score = RS = (I1 + I2 +...+ In) / n (I=Item, n=number of items)

Functional scales: 1 – [(RS – 1)/Range] x 100 (Range = difference between highest and lowest score).

Symptom scale items and global QoL = [(RS – 1)/Range] x 100

For example: If the RS for a scale is 3, on functional scale, the linear transformation will be 1 – (3-1)/3 x 100 = 1 – 2/3 x100 = 1/3x100 = 33.3, and on Global QoL scale it will be 3-1/6 x 100 = 2/6 x 100 = 100/3 = 33.3.

## Appendix SQR10: Consort diagram of SOCQER2



# Appendix SQR11: Summary of complete case analysis post hoc comparisons

[Summary of complete case general linear repeated measures models statistical tests: SCS type]

| PROMs scale | N | Within group effect (sphericity assumed) p value | Between group effect p value | Contrasting 6 weeks with 6 months p value | Contrasting 6 months with 12 months p value | Between SCS group post hoc comparisons with Bonferroni adjustment p value |
|---|---|---|---|---|---|---|
| **QLQ-C30** | | | | | | |
| Global QoL | 121 | <0.001 | 0.539 | <0.001 | 0.219 | ns |
| Physical function | 121 | <.001 | 0.009 | <0.001 | 0.001 | Low v high 0.009<br>Low v intermediate 1.000<br>Intermediate v high 0.061 |
| Role function | 131 | <0.001 | 0.070 | <0.001 | 0.114 | ns |
| Emotional function | 128 | 0.430 | 0.005 | 0.198 | 0.593 | Low v intermediate 1.000<br>low v high 0.004<br>intermediate v high 0.065 |
| Cognitive function | 129 | 0.732 | 0.731 | 0.509 | 0.919 | ns |
| Social function | 127 | <0.001 | 0.213 | <0.001 | 0.045 | ns |
| Fatigue | 132 | <0.001 | 0.798 | <0.001 | 0.007 | ns |
| Nausea | 130 | 0.030* | 0.336 | <0.016 | 0.312 | ns |
| Pain | 131 | <0.001 | 0.772 | 0.012 | 0.069 | ns |
| Dyspnoea | 126 | 0.468 | 0.837 | 0.399 | 0.240 | ns |
| Insomnia | 127 | 0.007 | 0.812 | 0.016 | 0.617 | ns |
| Appetite | 132 | <0.001* | 0.208 | <0.001 | 0.159 | ns |
| Constipation | 131 | <0.001* | 0.556 | <0.001 | 0.388 | ns |
| Diarrhoea | 131 | <0.079* | 0.204 | <0.023 | 0.880 | ns |
| Financial difficulty | 124 | 0.103* | 0.002 | 0.143 | 0.384 | Low v intermediate 0.048<br>Low v high 0.003<br>Intermediate v high 0.954 |
| **QLQ-OV28** | | | | | | |
| Abdominal pain | 189 | <0.001 | 0.142 | <0.001 | - | ns |
| Peripheral neuropathy | 129 | <0.001* | 0.837 | <0.001 | 0.007 | ns |
| Hormonal symptoms | 131 | 0.067 | 0.525 | 0.305 | 0.195 | ns |
| Body image | 131 | 0.001 | 0.396 | 0.045 | 0.099 | ns |
| Attitude to disease / treatment | 127 | 0.001 | 0.703 | 0.017 | 0.157 | ns |
| Chemotherapy side effects | 125 | 0.660 | 0.491 | 0.811 | 0.531 | ns |
| Other symptoms | 41 | 0.004 | 0.392 | 0.925 | 0.011 | ns |

*Mauchly's w p=0.005, Greenhouse- Geisser test used

# CHAPTER 4:
# INCIDENCE AND PREDICTORS OF ACUTE KIDNEY INJURY DURING TREATMENT FOR ADVANCED OVARIAN CANCER


## Abstract:

**Objective:** To investigate the incidence and predictors of AKI in patients undergoing surgical intervention and chemotherapy for advanced ovarian cancer.

**Design and Methods:** Multicentre, international, prospective observational study as a trainee led collaborative project linked to SOCQER-2 (Surgery in advanced ovarian cancer: quality of life evaluation research) study across 12 gynaecological cancer centres in the UK and Tata Memorial Hospital, Kolkata, India.

**Main Outcome Measures:** Incidence of AKI in patients undergoing surgery at peri-operative and late post-operative period, recurrence of AKI events, predictors of AKI and any effects in the management of ovarian cancer.

**Results:** 236 patient's data were included in the study. The overall incidence of AKI was 30.5% (n=72) in the study cohort, with 50 (21%) patients having "RIFLE-risk" or AKIN-1. 15 patients (6%) sustained "RIFLE-Injury" or AKIN-2 and 7 (3%) patients had "RIFLE-Failure" or AKIN-3 diagnosed during treatment. One patient needed to have renal replacement therapy. 21 (9%) patients had recurrent AKI during their treatment and up to 6 months post-surgery. The main predictors of AKI were ECOG performance status more than 0, Age-Adjusted Charlson's Co-morbidity Index of 2 or more, Body Mass Index more than 25, serum albumin level less than 35 and Peritoneal Carcinomatosis Index more than 12. Pre-operative

AKI diagnosis was associated with further recurrence of AKI. Perioperative AKI did not cause a significant delay in discharge from the hospital and did not delay postoperative chemotherapy.

**Conclusions:** Patients' preoperative characteristics such as age, BMI, albumin level, performance status and comorbidity index were associated with AKI events along with their disease burden. The extensiveness of surgery did not contribute to AKI events. Preoperative nutrition, comorbidity assessment and its management are important factors that, if managed well, could lead to the prevention of peri-operative and late post-operative AKI events.

Funding: University of Birmingham, Birmingham, United Kingdom.

Keywords: Acute Kidney Injury, AKI, Ovarian cancer, debulking surgery

## Introduction:

Acute kidney injury (AKI) is a common risk for the patients admitted to the hospital. Approximately 13 – 18% of the patients endure AKI while hospitalised and older people are at increased risk (National Clinical Guideline, 2013). The risk further increases with co-morbidities and can lead to serious complications. The associated morbidity and mortality in these patients are higher even if the extent of AKI is mild (Chertow et al., 2005, Uchino et al., 2010, Kork et al., 2015, Heung et al., 2016). Up to two-thirds of patients admitted to intensive care may develop AKI and in patients, requiring renal replacement therapy, the in-hospital mortality rate is 50 – 60%. Among survivors, 5 – 20% remain dependent on dialysis (Hoste and Schurgers, 2008). National Institute for Health and Care Excellence (NICE) states that AKI is 100 times more deadly than MRSA infection and estimates the cost of AKI to NHS between 434 million to £620 million per annum (National Clinical Guideline, 2013). In 2009, The National Confidential Enquiry into Patient's Outcome and Death (NCEPOD) found that 43% of the patients had delayed recognition of AKI and only about 50% of patients receive good care post-admission. The report also suggested that 21% of the cases of post-admission AKI were avoidable (MacLeod, 2009).

A single centre retrospective observational study evaluated the prevalence, outcomes and cost associated with AKI after the major gynaecological surgery between January 2000 and November 2010. The AKI was measured as per RIFLE (Risk, Injury, Failure, Loss, and End-stage) criteria. The data of 2341 patients were studied and an overall prevalence of 13% was reported. 1159 patients had surgery for malignant gynaecological conditions and the incidence of

AKI was 18% (211/1159) compared to 5% risk of AKI in surgery for benign conditions (43/801) ($p<0.001$). Overall, 15% of these AKI patients later developed renal failure and 3% required renal replacement therapy. Compared to total in hospital mortality and 90 day mortality of 0.9% and 1.7% respectively, in-hospital mortality rate was 7% and 90-day mortality was 10% in women who developed AKI during admission for surgery (Vaught et al., 2015). Several studies have confirmed the association between AKI with progression to chronic kidney disease, end-stage kidney disease and mortality suggesting even a short episode of AKI might contribute to long-term morbidity (Coca et al., 2009, Waikar and Winkelmayer, 2009). It is also important to recognise that the patients whose renal functions are already compromised remain at a significantly higher risk of developing end-stage kidney disease (Prescott et al., 2007).

Patients with advanced ovarian cancer are treated with radical abdomino-pelvic surgery and platinum based chemotherapy. In addition to cancer, other risk factors for AKI may be present in the patients with advanced ovarian cancer, such as older age, co-morbidities and treatment with platinum based chemotherapy, which is known to be nephrotoxic (Oun et al., 2018). The surgery for advanced ovarian cancer frequently involves longer operating time, major fluid shifts due to ascites or blood loss, ureteric dissection and intensive care unit admission. Despite having multiple risk factors, the incidence of AKI after ovarian cancer surgery has not been extensively investigated.

Surgery in Ovarian Cancer: Quality of life Evaluation Research (SOCQER-2) is a multicentre, prospective, exploratory, observational cohort study that has recruited patients with advanced ovarian cancer. The study aims to describe patient

reported outcomes (PRO) and surgical outcomes at 12 sites across the United Kingdom and one centre from Kolkata (India). An additional study to report the incidence and predictors of acute kidney injury during the management of advanced ovarian cancer was undertaken.

## Methods:

I planned this study and discussed with SOCQER-2 team. It was then discussed with the steering group committee and adopted as a trainee led collaborative project at the beginning of the recruitment of patients for SOCQER-2 was beginning. (Surgery in advanced Ovarian Cancer: Quality of life Evaluation Research, ethical approval from Solihull National Health Service Research Ethics Committee reference number 15/WM/0124, and ClinicalTrials.gov registration no: NCT02569983).

**Study population:** The study population included patients recruited for SOCQER-2 study across 12 centres in the United Kingdom and from a parallel study in Kolkata (India), from September 2015 to September 2016. All patients met eligibility criteria for SOCQER-2 study: patients with suspected or confirmed ovarian cancer, fallopian tube cancer or primary peritoneal cancer with FIGO stage III – IV, listed for either primary debulking surgery or neo-adjuvant chemotherapy with intention of delayed debulking surgery. All patients were considered eligible for AKI study except for those who either did not receive surgery or were proven to have early stage (I – II) / benign disease after surgery. Patients were also excluded if they had non-gynaecological cancer.

**Aims:** The primary aim of this study was to investigate incidence of AKI in the patients undergoing cytoreduction surgery for advanced ovarian cancer and to identify predictors of AKI in these patients.

**Study design and data collection:** The study paralleled the design of SOCQER-2: prospective, international, multi-centre and observational cohort study. Patients were identified and consented before intervention and followed up for the duration of study. I designed an additional case report form in consultation with SOCQER-2 team and a nephrology expert to capture relevant data at important time points during preoperative, immediate post-operative and late post-operative duration. These time points allowed capture of renal function test data at up to 8 points comprising the pre-operative duration, during neoadjuvant chemotherapy (NACT), immediately following cytoreduction surgery and between 6 weeks to 6 months during adjuvant chemotherapy, in order to understand the impact of all phases of treatment on development of AKI. Data on patient's age, performance status (PS), body mass index (BMI), timing of surgery, ascites / pleural effusion, age adjusted Charlson Co-morbidity Index, Peritoneal Carcinomatosis Index, surgical complexity, residual disease status, intensive care admission, post-operative morbidity, final FIGO stage, histological diagnosis, adjuvant chemotherapy and survival at 2 years post-surgery were extracted from SOCQER-2 case report forms. A designated trainee / nurse captured all the data required for the study at each centre. Missing data or data which were not entirely clear were queried and rechecked by SK.

**Identification and classification of AKI:** The Acute Dialysis Quality Initiative provides the RIFLE classification for AKI based on relative increase in serum

creatinine or drop in estimated glomerular filtration rate (eGFR) or measurement of urinary output over a period (Bellomo et al., 2004). The term AKI is a general description of renal compromise and includes the entire spectrum of syndrome from minor dysfunction to the requirement of renal replacement therapy (Kellum et al., 2008). The classification defines the injury in the short term (risk, injury, failure), whether reversible by timely intervention in management and on the long term basis (loss, end-stage), if the renal failure is still present at 4 weeks and 3 months respectively (Bellomo et al., 2004). This tool is accepted and validated in many studies in health care research (Hoste and Kellum, 2006a, Hoste and Kellum, 2006b). Further to this, the Acute Kidney Injury Network (AKIN) classification were proposed and widely adopted (Mehta et al., 2007), with exclusion of “Loss” and “End stage kidney disease” as described in RIFLE classification, and these were considered as outcome of AKI.

In this thesis, I used changes in the serum creatinine level at different time points and also evaluated changes in estimated glomerular filtration rate (eGFR) using “The Modification of Diet in Renal Disease (MDRD)” formula for this purpose. The option of measurement of urinary output to identify AKI events was eliminated at the planning phase due to anticipation of missing values, inaccurate recording and difficulty in data collection through case notes. In clinical practice, serum creatinine and eGFR are recorded routinely before and after the surgery and during administration of chemotherapy. Therefore, it remained an inexpensive way to collect data to investigate the incidence of AKI in a cohort of patients with ovarian cancer. If there were more than one test result available at one time-point, the worst value was taken into consideration as a marker of maximum change at that

particular time-point. If eGFR value was not available, it was calculated using the MDRD formula taking account of its limitations (Levey et al., 2006). Both RIFLE criteria and AKIN staging were used for the identification of AKI events. Pragmatically, Risk, Injury and Failure grading of RIFLE classification corresponded to AKIN 1, 2 and 3 respectively. eGFR calculation by MDRD formula did not provide any additional events of AKI.

**Statistical analysis:** SPSS V22 was used for analysis of data. Categorical data were expressed using proportions and associations were analysed using the Chi-square test. Differences in the mean of continuous variables were calculated using independent T-tests. Mean values were expressed with standard deviations and differences in the mean were provided with standard deviations. Multivariate analysis using a multiple logistic forward stepwise regression model was used to identify important predictor of all events of AKI and post-operative AKI. A p-value of $<0.05$ was considered to indicate statistical significance.

## Results:

A total of 293 patients were recruited for SOCQER-2 study between September 2015 to September 2016; 235 patients were from 12 UK centres and 58 patients were recruited from Kolkata, India. 236 patient's data were used for analysis of incidence of AKI. The reasons for exclusions are provided in Appendix AKI7, page 192.

The median age of patients was 63 years (IQR 16) and mean BMI of the cohort was 27 (SD 5.4). The mean pre-operative albumin level was 39 (SD 6.0). The Eastern Cooperative Oncology Group (ECOG) performance status was 0 or 1 for

210 (89%) patients. Seventy-two (30%) patients had primary debulking surgery and 164 (70%) patients had neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy. Aletti's surgical complexity scores were 1 – 3 (n=107, 45%), 4 – 7 (n=69, 29%) and >8 (n=60, 25%) respectively. Complete cytoreduction (no residual disease) was achieved for 147 (62%) patients and optimal cytoreduction (residual disease less than 1 cm) was achieved for 64 (27%) patients. Twenty five (11%) patients had sub-optimal cytoreduction (residual disease more than 1 cm). Clavian-Dindo grades 3 or 4 post-operative morbidities were observed for 30 (12.7%) patients and 2 (0.8%) patients died during post-operative period. Significant differences were present in the baseline characteristics between the UK and Kolkata patients: patients from Kolkata were younger, had higher disease load and a higher proportion of these patients underwent higher complexity surgery than UK patients. The differences are explained in the later section of this thesis and given in Table 29.

236 patients included in this study had their data analysed for peri-operative events of AKI. Overall 72 (30.5%) patients were observed to have AKI (Risk, injury or failure) with a total of 95 events. One patient had AKI at pre-surgery, post-surgery and later again during chemotherapy. The maximum severity of AKI were risk (n=50, 21%), injury (n=15, 6%) and failure (n=7, 3%) as per RIFLE criteria. None of the patients were observed to have loss of function or end stage renal disease during the peri-operative period (up to 6 weeks) and up to 6 months post-operative period. One patient received renal replacement therapy (haemodialysis) during the post-operative period. The characteristics of patients with and without AKI are given in Table 25 and Table 26.

28 (12%) patients had an AKI event pre-operatively, 26 (11%) had AKI during immediate post-operative period and among these 9 patients had AKI pre-operatively and post-operatively. A total of 39 (17%) patients had AKI in late post-operative period, during their chemotherapy. Of these 39 patients, 13 (33%) had AKI either during pre-operative or post-operative period. Only one patient had AKI during all three periods of observation, with normal recovery in between. Overall, among those 72 patients, who developed AKI during any phase of their treatment, 21 (29%) patients had recurrent AKI. Overall, 9% of our cohort of patients with ovarian cancer had recurrent episodes of AKI.

Statistically significant associations ($p<0.05$) between patient characteristics and all events of AKI during treatment were observed for patients with body mass index (BMI) more than 25 ($p=0.018$), ECOG performance status higher than 0 ($p=0.013$), Age-adjusted Charlson's Co-morbidity Index (ACCI) > 2 ($p=0.006$) and peritoneal carcinomatosis index (PCI) > 12 ($p=0.026$). Age (≤70 years or higher), BMI (≤25 or higher), ECOG PS (0 or higher), ACCI (≤2 or higher), preoperative albumin level (≤34 or higher) and PCI (≤12 or higher) were entered into a forward stepwise logistic regression model and in the final model BMI > 25 (OR 2.03, 95% CI 1.11 – 3.72), ACCI > 2 (OR 2.07, 95% CI 1.15 – 3.73) and PCI > 12 (OR 1.99, 95% CI 1.11 – 3.57) were found to be significant predictors of all events of AKI (Table 30).

With regard to all post-operative events of AKI, statistically significant associations ($p<0.05$) were observed for age more than 70 years ($p=0.022$), ECOG PS more than 0 ($p=0.039$), ACCI >2 ($p=0.001$), sub-optimal cytoreduction ($p=0.028$), Postoperative Clavien-Dindo grade 3 to 5 morbidity ($p=0.013$) and pre-operative

AKI (p<0.001). On sub-group analysis, pre-operative AKI was associated with immediately post-operative AKI (p=0.001). Age (≤70 years or higher), ECOG PS (0 or higher), ACCI (≤2 or higher), residual disease status (optimal vs sub-optimal) after surgery, morbidity grades as per Clavien-Dindo classification (up to 2 vs 3 and above), and pre-operative events of AKI (present vs none) were entered into a forward stepwise regression model and in the final model ACCI > 2 (OR 2.54, 95% CI 1.37 – 4.72) and pre-operative AKI (OR 4.39 95% CI 1.88 – 10.26) were predictors for post-operative AKI events (Table 30).

The AKI outcomes were assessed for increased length of hospital stay, surgery to chemotherapy interval of more than 6 weeks and the event of recurrent AKI after having AKI during peri-operative period. Patients with AKI in the whole cohort had 1 extra day stay in hospital (p=0.022) (Table 27). Surgery to adjuvant chemotherapy interval was not different in patients who had any AKI events during the peri-operative period. Recurrent AKI during late post-operative period (6 weeks to 6 months) was higher in patients who had AKI during peri-operative period, but it was not statistically significant (OR 2.03 95% CI 0.94 – 4.39).

Subgroup analysis of the UK patients and Kolkata patients was carried out to understand any differences in the population characteristics and AKI events (Appendices AKI 2 – 7, page 187 – 192). An overall risk for incurring AKI during treatment for advanced ovarian cancer was recorded as 30.5%. However, it was 26% in UK patients and 47% in Kolkata patients (OR 2.54, 95% CI 1.34 – 4.81, p=0.004). Patients recruited from Kolkata were significantly younger than UK patients and had less co-morbidities, however, their disease load (pre-operative peritoneal carcinomatosis index) was significantly higher and patients had higher

complexity surgery (p<0.001) (Table 28). In spite of use of higher complexity surgery, the proportion of patients, who received sub-optimal cytoreduction, were higher than UK cohorts, reflecting the differences in preoperative disease load. Table 29 demonstrates the difference between the two cohorts for events of AKI, their severity according to RIFLE criteria and timing of AKI events. The higher incidence of AKI in Kolkata patients was primarily due to higher events of "Risk – category" as per RIFLE criteria, occurring around peri-operative period (OR 3.192, 95%CI 1.58 – 6.46). There was no difference for late AKI during post-operative adjuvant chemotherapy (p=0.953) in between the two groups. UK patients showed an increased risk of recurrent AKI during immediate post-operative period (OR 5.84, 95% CI 2.07 – 16.50) and also during late post-operative period (OR 2.94, 95% CI 1.18 – 7.32), if they had pre-operative or peri-operative AKI respectively.

The analysis of association of post-operative AKI events and patient characteristics among Kolkata patients showed a significant association with lower Alleti's surgical complexity score of less than 7 (OR 2.64, 95% CI 1.18 – 5.92) and sub-optimal cytoreduction, reflecting the effect of disease burden. The timing of surgery (NACT vs PDS) and higher complexity of surgery was not associated with increased events of AKI. Even though, the incidences of AKI were higher, they were mainly "RIFLE – Risk" type and did not result in delay in surgery to adjuvant chemotherapy interval or events of recurrent AKI.

UK patients were 10 years older than Kolkata patients (64 vs 54 years, p=0.001) and they had higher ACCI (2.23 vs 1.39, p=0.001). However Kolkata patients had higher pre-operative PCI (18 vs 11, p=0.001) and they underwent higher complexity surgery (Aletti's score 11 vs 5, p=0.001). Due to these differences, the

location was entered as a predictive variable in forward stepwise regression model to predict AKI events. Not surprisingly, it emerged as a strong predictor for all AKI events (OR 3.93, 95% CI 1.90 – 8.15). When it was removed from the model, PCI >12 entered as a predictor, which were known to be significantly higher in Kolkata patients (Table 28). Overall, during the treatment of advanced ovarian cancer, patient's characteristics, such as ECOG performance status of ≥1, ACCI >2, preoperative albumin level <35 gm/L, BMI >25 and PCI >12 were all predictors for AKI during peri-operative and late post-operative period.

## Discussion:

Cancer patients are at increased risk of developing acute kidney injuries. A Danish population based study reported 1 year risk of AKI for advanced ovarian cancer as 27% (Christiansen et al., 2011). In spite of having multiple risk situations for renal function compromise during treatment for advanced ovarian cancer, such as extensive abdomino-pelvic surgery leading to major fluid shifts and platinum based chemotherapy (Oun et al., 2018), there is lack of information in the current literature regarding the actual incidence and impact of AKI in patients receiving treatment for advanced ovarian cancer, especially during the peri-operative and post-operative period. This is the first prospective, multicentre observational study to assess the risk of AKI during the treatment of advanced ovarian cancer, including preoperative, immediately post-operative and late post-operative period while the patient is undergoing surgical intervention and neoadjuvant or adjuvant chemotherapy.

This study observed a significant number of events of AKI during peri-operative and late post-operative period, including incidences of recurrent AKI. Seventy-two

patients (30.5%) sustained various degrees of AKI during the study duration and 21 (29%) of these patients had more than one episode of AKI. The analysis of factors contributing to these events was associated with patients' baseline characteristics. Extensiveness of surgical intervention and duration of surgery did not demonstrate a significant association with AKI in our study cohort. However, sub-optimal debulking (residual disease more than 1 cm) was associated with increased incidence of AKI, which reflects the effect of disseminated carcinomatosis. The differences in the AKI events and their pattern were noticeable between the UK and Kolkata patient cohorts, but it is not obvious if ethnicity, disease burden or some unknown confounding factors have causal associations with this. The Kolkata patients were 10 years younger and relatively fitter but had higher disease load. Reports have suggested that South Asian patients (Kolkata & Bangladesh), as in our study, are more susceptible for AKI events at a younger age (Feehally, 2003, Yang, 2016), however, it cannot be concluded as substantive evidence from this study and we cannot be sure, as there may be other unknown factors responsible for this finding.

Although 50 (21%) patients had the mildest form of AKI, described as "Risk" as per RIFLE criteria, 22 (10%) of them sustained more severe form of AKI such as "Injury" or "Failure". Meta-analysis and studies from other divisions of medicine has reported that even milder form of AKI is independently and significantly associated with longer hospital admission, associated complications and mortality in spite of partial or full recovery of renal function (Bihorac et al., 2009) and severity of these effects worsens along severity of AKI (See et al., 2019). Similarly, recurrent episodes of AKI are associated with chronic kidney disease and mortality

(Horne et al., 2017, Rodríguez et al., 2018). In our cohort, length of hospital stay and interval to chemotherapy after surgery were similar in both groups after the surgery. However, patients who had AKI in peri-operative period were more susceptible to sustain further episodes of AKI.

A limitation of this study is that we could not perform separate analysis of effects of diabetes, hypertension, intra-operative fluid management and use of NSAIDs during post-operative time outcomes. This was due to incomplete data collection on pre-operative morbidity and the design of the study in regard to intra-operative fluid management. This information is imperative and should be considered in such studies. However, I used Age-adjusted Charlson's Co-morbidity Index as a surrogate marker for pre-existing co-morbidities to analyse comorbidities and associated AKI events, which has been shown to predict AKI in critically ill patients (Talib et al., 2017). The relative numbers of patients with individual disease such as hypertension or diabetes were not enough in our population to be able to perform a meaningful analysis. Similarly, NSAIDs were used in under 20% of our study population and to show NSAID use as a predictor for AKI events, we would have needed a very large number of patients in the cohort. We did not have data on intra-operative and post-operative fluid management, which could have provided us further information. Another limitation is that centres included in the study may have selected patients according to their local policy and therefore variations in patient cohorts might exist.

This study provides meaningful information on perioperative AKI in an international multicentre setting as patients were prospectively selected and a wide range of data around treatment of ovarian cancer were utilised for analysis of predictors

and outcomes. The results demonstrate the importance of a careful watch over patients during their treatment including observing renal function test trends to pick up patients at risk. The result can be used to inform patients and health care providers about the risk of AKI during ovarian cancer treatment and targeted use might achieve a better outcome improving health care provision. This study did not investigate if incidence of AKI caused any dose modification, use of alternative chemotherapy or incomplete treatment which could have provided more information related to future chemotherapy, progression free survival or overall survival.

## Conclusions:

Patient related factors were associated more with events of AKI than surgery related factors. Therefore improving patient's nutrition, performance status and managing associated co-morbidities prior to surgical intervention could have potential to result in reduced post-operative AKI events. A pre-operative AKI event is a significant risk for recurrent AKI and identifying these patients will help in timely recognition and appropriate supportive management that would lead to prevention of further complications and can also help to plan individualised treatment of patients during their chemotherapy.

**Table 25: Patient characteristics and all incidence of AKI during treatment**

| All AKI events during treatment | | | | |
|---|---|---|---|---|
| | **All patients n (range)** | **Non AKI n (%)** | **AKI n (%)** | **P value / OR (95% CI)** |
| Age | | | | 0.113 OR 1.57 (0.90 – 2.74) |
| Up to 63 years* | 120 | 89 (74) | 31 (26) | |
| 64 and above | 116 | 75 (65) | 41 (35) | |
| | | | | |
| Body mass index | | | | 0.018 OR 2.012 (1.12 – 3.61) |
| Up to 25* | 103 | 80 (78) | 23 (22) | |
| More than 25 | 131 | 83 (63) | 48 (37) | |
| | | | | |
| Eastern Co-operative Oncology Group Performance status: | | | | 0.013 OR 2.08 (1.16 – 3.72) |
| 0 (Fully active)* | 104 | 81 (78) | 23 (22) | |
| 1, 2, 3 or 4 (Restricted activity) | 132 | 83 (63) | 49 (37) | |
| | | | | |
| Age adjusted Charlson Comorbidity Index: | | | | 0.006 OR 2.22 (1.26 – 3.91) |
| 0 – 2 (Mild)* | 149 | 113 (76) | 36 (24) | |
| 3 and above (Moderate or severe) | 87 | 51 (59) | 36 (41) | |
| | | | | |
| Preoperative albumin: | 40 (13 – 52) | 39 (13 – 52) | 37 (20 – 49) | 0.126 OR 0.60 (0.31 – 1.16) |
| Up to 34 g/L | 48 | 29 (60) | 19 (40) | |
| 35 g/L and above* | 188 | 135 (72) | 53 (28) | |
| | | | | |
| Baseline mean eGFR (SD) | 231 | 82 (10.7) | 72 (17) | <0.001 |
| | | | | |
| PDS / NACT: | | | | 0.767 OR 1.10 (0.60 – 2.01) |
| PDS* | 72 | 51 (71) | 21 (29) | |
| NACT | 164 | 113 (69) | 51 (30) | |
| | | | | |
| Ascites/Pleural effusion: | | | | 0.153 OR 1.55 (0.85 – 2.81) |
| Yes* | 67 | 42 (63) | 25 (37) | |
| No | 169 | 122 (72) | 47 (28) | |
| | | | | |
| Peritoneal Carcinomatosis Index | | | | 0.026 OR 1.89 (1.08 – 3.31) |
| Up to 12* | 137 | 103 (75) | 34 (25) | |
| 13 and above | 99 | 61 (62) | 38 (38) | |
| | | | | |
| | | | | |

[* Baseline variable against which OR is compared to. AKI = Acute kidney injury, OR=Odds ratio. PDS=Primary debulking surgery, NACT=Neoadjuvant chemotherapy.]

**Table 26: Patient characteristics and postoperative AKI**

| All Post-operative AKI events | | | | |
|---|---|---|---|---|
| | **All patients n (range)** | **Non AKI n (%)** | **AKI n (%)** | **P value / OR (95% CI)** |
| Age | | | | |
| Up to 63 years* | 177 | 96 (80) | 24 (20) | 0.071 OR 1.73 (0.95 – 3.14) |
| 64 and above | 59 | 81 (70) | 35 (30) | |
| | | | | |
| Body mass index | | | | 0.086 OR 1.73 (0.92 – 3.25) |
| Up to 25* | 96 | 77 (80) | 19 (20) | |
| More than 25 | 127 | 89 (70) | 38 (30) | |
| | | | | |
| Eastern Co-operative Oncology Group Performance status: | | | | 0.039 OR 1.89 (1.03 – 3.49) |
| 0 (Fully active)* | 104 | 84 (81) | 20 (19) | |
| 1, 2, 3 or 4 (Restricted activity) | 132 | 91 (69) | 41 (31) | |
| | | | | |
| Age adjusted Charlson Comorbidity Index: | | | | 0.001 OR 2.64 (1.45 – 4.80) |
| 0 – 2 (Mild)* | 149 | 121 (81) | 28 (19) | |
| 3 and above (Moderate or severe) | 87 | 54 (62) | 33 (38) | |
| | | | | |
| Preoperative albumin: | | | | 0.184 OR 0.629 (0.32 – 1.25) |
| Up to 34* | 48 | 32 (67) | 16 (33) | |
| 35 and above | 188 | 143 (76) | 45 (24) | |
| | | | | |
| PDS / NACT: | | | | 0.399 OR 1.32 (0.69 – 2.54) |
| PDS* | 72 | 56 (78) | 16 (22) | |
| NACT | 164 | 119 (73) | 45 (27) | |
| | | | | |
| Ascites/Pleural effusion: | | | | 0.123 OR 1.630 (0.87 – 3.03) |
| No* | 169 | 130 (77) | 39 (23) | |
| Yes | 67 | 45 (67) | 22 (33) | |
| | | | | |
| PCI | | | | 0.468 OR 1.243 (0.69 – 2.24) |
| Up to 12* | 137 | 104 (76) | 33 (24) | |
| 13 and above | 99 | 71 (72) | 28 (28) | |
| | | | | |
| Aletti's surgical complexity score: | | | | 0.238 |
| SCS 1 – 3 | 107 | 75 (70) | 32 (30) | |
| SCS 4 – 7 | 69 | 52 (75) | 17 (25) | |
| SCS ≥ 8 | 60 | 37 (62) | 23 (38) | |
| | | | | |
| Duration of surgery: | | | | 0.095 OR 1.665 (0.91 – 3.03) |
| Up to 5 hours* | 156 | 121 (78) | 35 (22) | |
| More than 5 hours | 80 | 54 (68) | 26 (32) | |
| | | | | |
| Outcome of surgery: | | | | 0.028 OR 2.53 (1.08 – 5.93) |
| Complete or optimal (< 1cm) cytoreduction achieved * | 211 | 161 (76) | 50 (24) | |
| Sub-optimal cytoreduction (> 1 cm residual disease) | 25 | 14 (56) | 11 (44) | |

| | | | | |
|---|---|---|---|---|
| Number of days in ITU: | | | | 0.091 OR 1.697 (0.92 – 3.15) |
| 0 – 1 days* | 167 | 129 (77) | 38 (23) | |
| 2 or more days | 69 | 46 (67) | 23 (33) | |
| | | | | |
| Postoperative complications grade: | | | | 0.013 OR 2.598 (1.20 – 5.61) |
| Clavien-Dindo grade 0 – 2* | 204 | 157 (77) | 47 (23) | |
| Clavien-Dindo grade 3 - 5 | 32 | 18 (56) | 14 (44) | |
| | | | | |
| Pre-operative AKI | | | | 0.001 OR 4.06 (1.81 – 9.15) |
| No preoperative AKI* | 208 | 162 (78) | 46 (22) | |
| Preoperative AKI present | 28 | 13 (46) | 15 (54) | |
| | | | | |

[* Baseline variable against which OR is compared to. AKI = Acute kidney injury, OR=Odds ratio. PDS=Primary debulking surgery, NACT=Neoadjuvant chemotherapy, PCI=Peritoneal carcinomatosis index, ITU=Intensive treatment unit.]

**Table 27: AKI and associated outcomes**

| Outcomes of Perioperative AKI | All patients n (range) | Non AKI n (%) | AKI n (%) | P value / OR (95% CI) |
|---|---|---|---|---|
| Length of hospital stay | 6 (1 – 69) | 6 (1 – 69) | 7 (3 – 39) | 0.022 OR (1.11 – 4.30) |
| Up to 6 days | 122 | 106 (87) | 16 (13) | |
| 7 days and more | 113 | 85 (75) | 28 (25) | |
| | | | | |
| Surgery to chemotherapy interval | | | | 0.669 OR 0.838 (0.37 – 1.89) |
| Up to 42 days | 179 | 134 (75) | 45 (25) | |
| 43 days and more | 41 | 32 (78) | 9 (22) | |
| | | | | |
| Recurrent AKI during postoperative chemotherapy | | | | 0.042 OR 2.21 (1.02 – 4.80) |
| No perioperative AKI* | 197 | 164 (83) | 33 (17) | |
| Perioperative AKI present | 39 | 27 (69) | 12 (31) | |
| | | | | |

[AKI=Acute kidney injury, OR=Odds ratio, CI=Confidence interval]

**Table 28: Difference between patients Characteristic from Kolkata and UK centres**

| Participant's Characteristic | UK participants (n=185), mean (SD) | Kolkata participants (n=51), mean (SD) | P-value |
|---|---|---|---|
| Age | 63.6 (10.9) | 53.8 (10.6) | 0.001 |
| BMI | 27.6 (5.6) | 26.9 (4.3) | 0.873 |
| Preoperative Haemoglobin | 114 (16.5) | 107 (14.2) | 0.005 |
| Preoperative albumin | 38.4 (6.4) | 40.5 (3.8) | 0.025 |
| Age adjusted Charlson's comorbidity index | 2.23 (1.3) | 1.39 (1.1) | 0.001 |
| Preoperative PCI | 10.6 (7.5) | 17.6 (9.5) | 0.001 |
| Aletti's surgical complexity score | 4.5 (3.2) | 10.5 (6.8) | 0.001 |
| Number of days in ITU | 1.01 (3.3) | 3.02 (4.7) | 0.067 |
| Length of hospital stay | 7.65 (7.3) | 9.75 (6.6) | 0.001 |
| Surgery to Chemotherapy interval | 36.2 (15.8) | 32.6 (10.7) | 0.128 |

[PCI=Peritoneal carcinomatosis index, ITU=Intensive treatment unit]

Table 29: Summary of AKI events, its severity, timing of events and differences in UK and Kolkata cohorts

| AKI incidence, severity and timing of AKI | Total UK & Kolkata combined, n=236 n (%) | UK patients only, n=185 n (%) | Kolkata patients only, n=51 n (%) | p value | OR (95% CI) |
|---|---|---|---|---|---|
| **Overall incidence of AKI** | 72 (30.5) | 48 (26) | 24 (47) | 0.004 | 2.537 (1.34 – 4.81) |
| **Category - Risk** | 50 (21.2) | 31 (16.8) | 19 (37.3) | 0.002 | 2.950 (1.49 – 5.86) |
| **Category - Injury** | 15 (6.4) | 11 (5.9) | 4 (7.8) | 0.623 | 1.346 (0.41 – 4.42) |
| **Category - Failure** | 7 (3) | 6 (3.2) | 1 (2) | 0.633 | 0.597 (0.70 – 5.07) |
| **Pre-operative AKI** | 28 (11.9) | 17 (9.2) | 11 (21.6) | 0.015 | 2.718 (1.18 – 6.25) |
| **Immediate post-operative AKI** | 26 (11) | 16 (8.6) | 10 (19.6) | 0.027 | 2.576 (1.09 – 6.09) |
| **Late post-operative AKI** | 39 (17) | 30 (16.2) | 9 (17.6) | 0.953 | 1.025 (0.45 – 2.31) |
| **Peri-operative AKI** | 45 (19.1) | 27 (14.6) | 18 (35.3) | 0.001 | 3.192 (1.58 – 6.46) |
| **All post-operative AKI** | 59 (25) | 41 (22.2) | 18 (35.3) | 0.082 | 1.801 (0.92 – 3.51) |

[AKI- Acute kidney injury, UK=United Kingdom, OR=Odds ratio, CI=Confidence interval]

Table 30: Multi-variate analysis (Logistic forward stepwise regression)

| | Adjusted Odds Ratio | 95% C.I. or adj. OR | |
|---|---|---|---|
| | | Lower | Higher |
| **All events of AKI in entire cohort** | | | |
| **BMI (≥25 compared to BMI <25)** | 2.03 | 1.11 | 3.72 |
| **ACCI (≥2 compared to ≤2)** | 2.07 | 1.15 | 3.73 |
| **PCI (≥12 vs <12)** | 1.99 | 1.11 | 3.57 |
| | | | |
| **Post-operative AKI in entire cohort** | | | |
| **ACCI (≥2 compared to ≤2)** | 2.54 | 1.37 | 4.72 |
| **Pre-operative event of AKI** | 4.39 | 1.88 | 10.26 |
| | | | |
| **All events of AKI in UK cohort** | | | |
| **ECOG PS (0 vs ≥1)** | 2.736 | 1.324 | 5.653 |
| **Pre-operative albumin (≥35 vs <35)** | .410 | .194 | .867 |
| | | | |
| **Post-operative AKI in UK cohort** | | | |
| **Age (>70 vs ≤70 years)** | 2.57 | 1.21 | 5.49 |
| **Pre-operative AKI (present vs not present)** | 6.41 | 2.11 | 19.42 |

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## Appendix AKI1: Patient characteristics and all incidence of AKI during treatment: UK patients

| All events of AKI during treatment | | | | |
|---|---|---|---|---|
| | **All patients n** | **Non AKI n (%)** | **AKI n (%)** | **P value / OR (95% CI)** |
| Age | | | | 0.042 OR 2.045 (1.01 – 4.10) |
| Up to 63 years* | 81 | 66 (82) | 15 (18) | |
| 64 and above | 104 | 71 (68) | 33 (32) | |
| | | | | |
| Body mass index | | | | 0.260 OR 1.475 (0.75 – 2.90) |
| Up to 25* | 83 | 65 (78) | 18 (22) | |
| More than 25 | 100 | 71 (71) | 29 (29) | |
| | | | | |
| Eastern Co-operative Oncology Group Performance status: | | | | 0.001 OR 3.11 (1.54 – 6.33) |
| 0 (Fully active)* | 91 | 77 (85) | 14 (15) | |
| 1, 2, 3 or 4 (Restricted activity) | 94 | 60 (64) | 34 (36) | |
| | | | | |
| Age adjusted Charlson Comorbidity Index: | | | | 0.002 OR 2.83 (1.44 – 5.57) |
| 0 – 2 (Mild)* | 108 | 89 (82) | 19 (18) | |
| 3 and above (Moderate or severe) | 77 | 48 (62) | 29 (38) | |
| | | | | |
| Preoperative albumin | | | | 0.006 OR 0.375 (0.18 – 0.77) |
| Up to 34 g/L* | 46 | 27 (59) | 19 (41) | |
| 35 g/L and above | 139 | 110 (79) | 29 (21) | |
| | | | | |
| PDS / NACT | 45 | 36 (80) | 9 (20) | 0.296 OR 1.544 (0.68 – 3.50) |
| PDS* | 140 | 101 (72) | 39 (28) | |
| NACT | | | | |
| | | | | |
| Ascites/Pleural effusion | | | | 0.103 OR 1.771 (0.89 – 3.53) |
| Yes* | 129 | 100 (78) | 29 (22) | |
| No | 56 | 37 (66) | 19 (33) | |
| | | | | |
| Peritoneal Carcinomatosis Index | | | | 0.05 OR 1.945 (1.00 – 3.80) |
| Up to 12* | 118 | 93 (79) | 25 (21) | |
| 13 and above | 67 | 44 (66) | 23 (34) | |
| | | | | |

[* Baseline variable against which OR is compared to. AKI = Acute kidney injury, OR=Odds ratio. PDS=Primary debulking surgery, NACT=Neoadjuvant chemotherapy.]

# Appendix AKI2: Patient characteristics and post-operative incidence of AKI: UK patients only

| Events Of all Post-operative AKI | | | | |
|---|---|---|---|---|
| | **All patients n** | **Non AKI n (%)** | **AKI n (%)** | **P value / OR (95% CI)** |
| Age | | | | 0.09 OR 1.85 (0.40 – 3.79) |
| Up to 63 years* | 81 | 67 (83) | 14 (17) | |
| 64 and above | 104 | 75 (72) | 29 (28) | |
| | | | | |
| Body mass index | | | | 0.065 OR 1.364 (0.68 – 2.74) |
| Up to 25* | 83 | 66 (80) | 17 (20) | |
| More than 25 | 100 | 74 (74) | 26 (26) | |
| | | | | |
| Eastern Co-operative Oncology Group Performance status: | | | | 0.013 OR 2.454 (1.20 – 5.03) |
| 0 (Fully active)* | 91 | 77 (85) | 14 (15) | |
| 1, 2, 3 or 4 (Restricted activity) | 94 | 65 (69) | 29 (31) | |
| | | | | |
| Age adjusted Charlson Comorbidity Index: | | | | 0.004 OR 2.729 (1.35 – 5.50) |
| 0 – 2 (Mild)* | 108 | 91 (84) | 17 (16) | |
| 3 and above (Moderate or severe) | 77 | 51 (66) | 26 (34) | |
| | | | | |
| Preoperative albumin | | | | 0.033 OR 0.452 (0.22 – 0.95) |
| Up to 34 g/L* | 46 | 30 (65) | 16 (35) | |
| 35 g/L and above | 139 | 112 (81) | 27 (19) | |
| | | | | |
| PDS / NACT | | | | 0.318 OR 1.542 (0.66 – 3.62) |
| PDS* | 45 | 37 (82) | 8 (18) | |
| NACT | 140 | 105 (75) | 35 (25) | |
| | | | | |
| Ascites/Pleural effusion | | | | 0.258 OR1.511 (0.74 – 3.10) |
| No* | 129 | 102 (79) | 27 (20) | |
| Yes | 56 | 40 (71) | 16 (29) | |
| | | | | |
| PCI | | | | 0.215 OR 1.55 (0.77 – 3.11) |
| Up to 12* | 118 | 94 (80) | 24 (20) | |
| 13 and above | 67 | 48 (72) | 19 (28) | |
| | | | | |
| Aletti's surgical complexity score | | | | 0.403 OR 1.444 (0.61 – 3.43) |
| Up to 7* | 154 | 120 (78) | 34 (22) | |
| 8 and above | 31 | 22 (71) | 9 (29) | |
| | | | | |
| Duration of surgery | | | | 0.403 OR 1.444 (0.61 – 3.43) |
| Up to 5 hours* | 154 | 120 (78) | 34 (22) | |
| More than 5 hours | 31 | 22 (71) | 9 (29) | |
| | | | | |
| Outcome of surgery | | | | 0.527 OR 1.452 (0.47 – 4.30) |
| Optimal cytoreduction achieved (R0 & <1cm)* | 168 | 130 (77) | 38 (23) | |
| Sub-optimal cytoreduction (> 1 cm) | 17 | 12 (71) | 5 (29) | |
| | | | | |
| Number of days in ITU | | | | 0.210 |

| | | | | |
|---|---|---|---|---|
| 0 – 1 days* | 146 | 115 (79) | 31 (21) | OR 1.649 (0.75 – 3.62) |
| 2 or more days | 39 | 27 (69) | 12 (31) | |
| | | | | |
| Postoperative complications grade | | | | 0.060 OR 2.476 (0.94 – 6.53) |
| Clavien-Dindo grade 0-2* | 165 | 130 (79) | 35 (21) | |
| Clavien-Dindo grade 3-5 | 20 | 12 (60) | 8 (40) | |
| | | | | |
| Pre-operative AKI | | | | <0.001 OR 5.844 (2.07 – 16.50) |
| No preoperative AKI* | 168 | 135 (80) | 33 (20) | |
| Preoperative AKI present | 17 | 7 (41) | 10 (59) | |
| | | | | |

[* Baseline variable against which OR is compared to. AKI = Acute kidney injury, OR=Odds ratio. PDS=Primary debulking surgery, NACT=Neoadjuvant chemotherapy, PCI=Peritoneal carcinomatosis index, ITU=Intensive treatment unit.]

## Appendix AKI3: AKI and associated outcomes for UK patients

| Outcomes of Perioperative AKI | All patients n (range) | Non AKI n (%) | AKI n (%) | P value / OR (95% CI) |
|---|---|---|---|---|
| Length of hospital stay | | | | 0.067 OR 2.168 (0.94 – 5.03) |
| **Up to 6 days** | 108 | 97 (90) | 11 (10) | |
| **7 days and more** | 76 | 61 (80) | 15 (20) | |
| | | | | |
| Surgery to chemotherapy interval | | | | 0.860 OR 0.915 (0.34 – 2.47) |
| **Up to 42 days** | 125 | 107 (86) | 18 (14) | |
| **43 days and more** | 45 | 39 (87) | 6 (13) | |
| | | | | |
| Recurrent AKI during postoperative chemotherapy | | | | 0.017 OR 2.935 (1.18 – 7.32) |
| **No perioperative AKI*** | 153 | 135 (88) | 18 (12) | |
| **Perioperative AKI present** | 32 | 23 (72) | 9 (28) | |
| | | | | |

[AKI=Acute kidney injury, OR=Odds ratio, CI=Confidence interval]

## Appendix AKI4: Patient characteristics and all incidence of AKI during treatment: Kolkata patients only

| All events of AKI during treatment | | | | |
|---|---|---|---|---|
| | **All patients n (range)** | **Non AKI n (%)** | **AKI n (%)** | **P value / OR (95% CI)** |
| Age | | | | 0.120 OR 2.875 (0.74 – 11.19) |
| Up to 63 years* | 39 | 23 (59) | 16 (41) | |
| 64 and above | 12 | 4 (33) | 8 (67) | |
| | | | | |
| Body mass index | | | | 0.011 OR 4.750 (1.37 – 16.47) |
| Up to 25* | 20 | 15 (75) | 5 (25) | |
| More than 25 | 31 | 12 (39) | 19 (61) | |
| | | | | |
| Eastern Co-operative Oncology Group Performance status: | | | | 0.064 OR 0.290 (0.75 – 1.11) |
| 0 (Fully active)* | 13 | 4 (31) | 9 (69) | |
| 1, 2, 3 or 4 (Restricted activity) | 38 | 23 (60) | 15 (40) | |
| | | | | |
| Age adjusted Charlson Comorbidity Index: | | | | 0.105 OR 3.294 (0.74 – 14.59) |
| 0 – 2 (Mild)* | 41 | 24 (58) | 17 (42) | |
| 3 and above (Moderate or severe) | 10 | 3 (30) | 7 (70) | |
| | | | | |
| Preoperative albumin: | | | | 0.174 OR 1.96 (1.49 – 2.58) |
| Up to 34 g/L* | 2 | 2 (100) | NA | |
| 35 g/L and above | 49 | 25 (51) | 24 (49) | |
| | | | | |
| PDS / NACT: | | | | 0.692 OR 1.250 (0.42 – 3.77) |
| PDS* | 27 | 15 (56) | 12 (44) | |
| NACT | 24 | 12 (50) | 12 (50) | |
| | | | | |
| Ascites/Pleural effusion: | | | | 0.574 OR 1.46 (0.38 – 5.60) |
| Yes* | 40 | 22 (55) | 18 (45) | |
| No | 11 | 5 (45) | 6 (55) | |
| | | | | |
| Peritoneal Carcinomatosis Index | | | | 0.973 OR 0.980 (0.31 – 3.06) |
| Up to 12* | 19 | 10 (53) | 9 (47) | |
| 13 and above | 32 | 17 (53) | 15 (47) | |
| | | | | |
| | | | | |

[* Baseline variable against which OR is compared to. AKI = Acute kidney injury, OR=Odds ratio. PDS=Primary debulking surgery, NACT=Neoadjuvant chemotherapy.]

# Appendix AKI5: Patient characteristics and post-operative incidence of AKI: Kolkata patients only

| Events Of all Post-operative AKI | | | | |
|---|---|---|---|---|
| | **All patients n (range)** | **Non AKI n (%)** | **AKI n (%)** | **P value / OR (95% CI)** |
| Age | | | | 0.009 OR 5.80 (1.43 – 23.50) |
| Up to 63 years* | 39 | 29 (74) | 10 (26) | |
| 63 and above | 12 | 4 (33) | 8 (67) | |
| | | | | |
| Body mass index | | | | 0.217 OR 2.167 (0.63 – 7.47) |
| Up to 25* | 20 | 15 (75) | 5 (25) | |
| More than 25 | 31 | 18 (58) | 13 (42) | |
| | | | | |
| Eastern Co-operative Oncology Group Performance status: | | | | 0.343 OR 0.538 (0.15 – 1.95) |
| 0 (Fully active)* | 13 | 7 (54) | 6 (46) | |
| 1, 2, 3 or 4 (Restricted activity) | 38 | 26 (68) | 12 (32 | |
| | | | | |
| Age adjusted Charlson Comorbidity Index: | | | | 0.010 OR 6.364 (1.39 – 29.06) |
| 0 – 2 (Mild)* | 41 | 30 (73) | 11 (27) | |
| 3 and above (Moderate or severe) | 10 | 3 (30) | 7 (70) | |
| | | | | |
| Preoperative albumin: | | | | 0.287 OR 1.581 (1.28 – 1.96) |
| Up to 34 g/L* | 2 | 2 (100) | NA | |
| 35 g/L and above | 49 | 31 (63) | 18 (37) | |
| | | | | |
| PDS / NACT: | | | | 0.369 OR 1.696 (0.53 – 5.40) |
| PDS* | 27 | 19 (70) | 8 (30) | |
| NACT | 24 | 14 (58) | 10 (42) | |
| | | | | |
| Ascites/Pleural effusion: | | | | 0.131 OR 2.80 (0.71 – 10.98) |
| No* | 40 | 28 (70) | 12 (30) | |
| Yes | 11 | 5 (46) | 6 (54) | |
| | | | | |
| PCI | | | | 0.164 OR 0.435 (0.13 – 1.42) |
| Up to 12* | 19 | 10 (53) | 9 (47) | |
| 13 and above | 32 | 23 (72) | 9 (28) | |
| | | | | |
| Aletti's surgical complexity score: | | | | 0.012 OR 0.217 (0.06 – 0.74) |
| Up to 7* | 22 | 10 (46) | 12 (54) | |
| 8 and above | 29 | 23 (79) | 6 (21) | |
| | | | | |
| Duration of surgery: | | | | 0.657 OR 0.531 (0.31 – 9.03) |
| Up to 5 hours* | 2 | 1 (50) | 1 (50) | |
| More than 5 hours | 49 | 32 (65) | 17 (35) | |
| | | | | |
| Outcome of surgery: | | | | 0.010 OR 7.750 (1.37 – 43.86) |
| Optimal cytoreduction achieved (R0 & <1cm)* | 43 | 31 (72) | 12 (28) | |
| Sub-optimal cytoreduction (> 1 cm) | 8 | 2 (25) | 6 (75) | |
| | | | | |
| Number of days in ITU: | | | | 0.806 |

| | | | | |
|---|---|---|---|---|
| 0 – 1 days* | 21 | 14 (67) | 7 (33) | OR 1.158 (0.36 – 3.74) |
| 2 or more days | 30 | 19 (63) | 11 (37) | |
| | | | | |
| Postoperative complications grade: | | | | 0.223 OR 2.25 (0.60 – 8.42) |
| Clavien-Dindo grade 0 – 2* | 39 | 27 (69) | 12 (31) | |
| Clavien-Dindo grade 3 - 5 | 12 | 6 (50) | 6 (50) | |
| | | | | |
| Post-operative AKI | | | | 0.426 OR 1.731 (0.45 – 6.74) |
| No preoperative AKI* | 40 | 27 (68) | 13 (32) | |
| Preoperative AKI present | 11 | 6 (55) | 5 (45) | |
| | | | | |

[* Baseline variable against which OR is compared to. AKI = Acute kidney injury, OR=Odds ratio. PDS=Primary debulking surgery, NACT=Neoadjuvant chemotherapy, PCI=Peritoneal carcinomatosis index, ITU=Intensive treatment unit.]

## Appendix AKI6: AKI and associated outcomes for Kolkata patients

| Outcomes of Perioperative AKI | All patients n (range) | Non AKI n (%) | AKI n (%) | P value / OR (95% CI) |
|---|---|---|---|---|
| Length of hospital stay | | | | 0.375 OR 0.571 (0.17 – 1.98) |
| Up to 6 days | 14 | 6 (43) | 8 (57) | |
| 7 days and more | 37 | 21 (57) | 16 (43) | |
| | | | | |
| Surgery to chemotherapy interval | | | | 0.918 OR 0.926 (0.22 – 3.95) |
| Up to 42 days | 41 | 22 (54) | 19 (46) | |
| 43 days and more | 9 | 5 (56) | 4 (44) | |
| | | | | |
| Recurrent AKI during postoperative chemotherapy | | | | 0.892 OR 0.900 (0.20 – 4.12) |
| No preoperative AKI* | 42 | 27 (64) | 15 (36) | |
| Preoperative AKI present | 9 | 6 (67) | 3 (33) | |
| | | | | |

[AKI=Acute kidney injury, OR=Odds ratio, CI=Confidence interval]

## Appendix AKI7: Reasons for exclusion from AKI cohort:

| Reasons | Number of patients | Percentage (%) |
|---|---|---|
| Benign/Borderline | 4 | 7.0 |
| Inoperable | 13 | 22.8 |
| Low stage | 15 | 26.3 |
| No data received | 11 | 19.3 |
| No Surgery | 7 | 12.3 |
| Not ovarian cancer | 5 | 8.8 |
| Withdrew consent | 2 | 3.5 |
| Total | 57 | 100.0 |

# CHAPTER 5:
# GENERAL DISCUSSION AND FUTURE IMPLICATIONS

The role of surgery in advanced ovarian cancer has been well established for many decades. The background literature review discussed in the introduction chapter clearly shows that complete debulking is associated with significantly improved progression free survival and overall survival and therefore the primary aim of surgical intervention in advanced ovarian cancer is to achieve no macroscopic residual disease. However, other determinant factors such as preoperative disease load and patient's comorbidities are also important in planning and delivering the treatment. Randomised controlled trials provide evidence for NACT followed by delayed debulking surgery is not inferior to PDS and in fact diminishes intraoperative and postoperative morbidity and particularly beneficial in patients with higher disease burden and FIGO stage 4 disease. To achieve complete debulking, extensive surgery involving upper abdominal disease / organ resection in addition to hysterectomy, salpingo-oophorectomy, omentectomy, peritonectomy and single or multiple bowel resections may still be necessary, whether patients are receiving PDS or NACT followed by debulking surgery. However, need for such extensive surgeries are lower with NACT followed by debulking surgery. The morbidities reported vary with different centres and types of surgeries performed, but these are not uniformly and extensively discussed in published literature compared to information on survival outcomes.

The impact on QoL following surgical intervention in advanced ovarian cancer is rarely reported.

The systematic review described in Chapter 2 focussed on compiling the available evidence on QoL outcomes during treatment in advanced ovarian cancer, where surgical intervention and characteristics of surgeries were provided. While QoL outcomes are usually reported in chemotherapy trials, it is sparsely discussed after surgical intervention. Only five studies fulfilled criteria for inclusion, including 3 randomised controlled trials and 2 observational studies reported on patient's QoL using EORTC QLQ-C30 +/- OV28 based on timing (PDS vs NACT followed by surgery) and extensiveness (standard or extensive) respectively. The meta-analysis of RCTs favoured a better QoL for NACT patients at $6^{th}$ cycle of chemotherapy, but no differences in QoL were observed at 6 months and 12 months. However, there was evidence of missing data due to substantial loss to follow-up. The two observational studies reporting on QoL comparing standard surgery to extensive surgery had small cohorts and evidence of selection bias leading to no convincing inference. The systematic review concluded that our current knowledge on QoL after surgery in advanced ovarian cancer is limited and potentially confounded and, specifically, the QoL of patients after extensive surgery is unknown.

Chapter 3 discusses our international, multicentre, prospective observational study: Surgery in advanced Ovarian Cancer: Quality of life Evaluation Research (SOCQER-2). We have shown that a high quality study on patient reported outcomes after surgery in advanced ovarian cancer is possible and well accepted by patients and organisations. The study data demonstrate that patient selection,

surgical approach and extensiveness of surgery vary across participating centres. Patients have better progression free and overall survival at 2 years if complete debulking was achieved at surgery. Among study groups based on extensiveness of surgery, the patients in intermediate surgical complexity group performed significantly better than low complexity and high complexity group of patients both in survival and QoL outcomes. This implies that patients with relatively lower disease burden when treated with maximal efforts during debulking surgery have significant benefits from the surgery. Patients with high preoperative disease load cannot be compared to those patients with lower preoperative disease load directly, but the QoL and survival outcomes were similar to those patients who had lower disease load at surgery and received low complexity surgery.

QoL of patients undergoing extensive surgery were not different than those having less extensive surgery except for physical function and role function domains of functional quality of life for a short period of time and with recovery to similar levels as patients undergoing less extensive surgery by 6 months. On symptom scales, no major differences were observed in between the groups at any given time points post-operatively except for financial problems for higher SCS type group, which were present prior to surgery and remained significant post-surgery. Peripheral neuropathy was the most commonly reported symptom even beyond 12 months in all groups of patients.

Our results also show that there were no detrimental effects of surgery in high SCS group relative to other groups within the study and in comparison to other published literature where similar procedures were undertaken. The mortality rate

related to surgery is consistent with other published studies for surgical intervention in advanced ovarian cancer.

Chapter 4 specifically explored the incidence and predictive factors for sustaining AKI in this cohort of patients. A total of 30% patients sustained AKI during treatment for advanced ovarian cancer either during chemotherapy or in postoperative period. About 10% patients had more than one episode of AKI. Extensiveness of surgery was not found to be associated with increased AKI events, but these AKI events were associated with patient's age, performance status, serum albumin level and comorbidities. However, most of these AKI events were transient and did not obviously affect the treatment. Whether these AKI events had any further deleterious effects on use of chemotherapy agents, schedule, dosage or late effects on patients' health is beyond the scope of this thesis.

In summary, our research show that wide variation in treatment for advanced ovarian cancer exist across centres including variation in selecting patients for surgical debulking and variation in extensiveness of surgical debulking. As a result, there is no uniformity in surgical outcome. Extensive surgery is not shown to be associated with significantly raised intraoperative or postoperative morbidities and the global QoL of these patients were not worse than patients having less extensive surgery.

**Clinical implications:** The results from this study should inform and reassure the patients, clinicians and policy makers that extensive surgery in advanced ovarian cancer is not associated with long-term deleterious effects on patient's health and QoL. Policies should support judicious and monitored use of multi-disciplinary

input for extensive debulking surgery with aim to achieve complete cytoreduction or even centralisation in higher volume centres in an attempt to reduce variation in case selection and surgical intervention. Only then, would surgical training and expertise flourish to enable us to improve our patient's survival.

**Research implications:** Centres providing surgical care for patients with advanced ovarian cancer should keep and monitor high quality data on surgical intervention, surgical outcome and patient reported outcomes. Development of a uniform data collection tool should be encouraged and made available for use by each centre. Further research in surgical trials should include PRO in the mainstream outcome measures using appropriate tools for the context. A similar prospective study including all centres in the UK could provide further robust evidence on surgical variations, outcomes and QoL of patients.

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