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DOI:
10.1111/1471-0528.17041

Quality of life from cytoreductive surgery in advanced Ovarian cancer: investigating association with disease burden and surgical complexity in the international, prospective, SOCQER2 cohort study

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Running title
Quality of life after surgery for ovarian cancer

Abstract 245 words excluding headings

Objective To investigate quality of life (QoL) and association with surgical complexity and disease burden after surgical resection for advanced ovarian cancer in centres with variation in surgical approach

Design Prospective multicentre observational study

Setting United Kingdom, Kolkata, India, and Melbourne, Australia gynaecological cancer surgery centres.

Participants Patients undergoing surgical resection for late stage ovarian cancer.

Exposure Low, intermediate or high Surgical Complexity Score (SCS) surgery

Main outcomes and measures Primary: EORTC-QLQ-C30 Global score change. Secondary: EORTC OV28, progression free survival.

Results Patients' pre-operative disease burden and SCS varied between centres, confirming differences in surgical ethos. QoL response rates were 90% up to 18 months. Mean change from the pre-surgical baseline in the EORTC QLQ-C30 was 3.4 (SD 1.8, n=88) in the low, 4.0 (SD 2.1, n=55) in the intermediate and 4.3 (SD 2.1, n=52) in the high SCS group after 6 weeks (p=0.048) and 4.3 (SD 2.1, n=51), 5.1 (SD 2.2, n=41) and 5.1 (SD 2.2, n=35) respectively after 12 months (p=0.133). In a repeated measures model, there were no clinically or statistically meaningful differences in EORTC QLQ-C30 global scores between the three SCS groups, p= 0.840 but there was a small statistically significant improvement in all groups over time (p<0.001). The high SCS group experienced small to moderate decreases in physical (p=0.004), role (p=0.016) and emotional (p=0.001) function at 6 weeks post-surgery which resolved by 6-12 months.

Conclusions and relevance Global QoL of patients undergoing low, intermediate, and high SCS surgery improved at 12 months post operation and was no worse in patients undergoing extensive surgery.

Tweetable abstract

Extensive surgery compared to lower complexity surgery does not result in poorer quality of life in patients with advanced ovarian cancer.

Introduction

Management of advanced ovarian cancer (stage III and IV) comprises cytoreductive surgery and systemic treatment. [1-3] Multiple studies have shown improved progression free survival (PFS) and overall survival (OS) where complete macroscopic cytoreduction has achieved no visible residual disease after resection.[4] Extensive surgery with a high Surgical Complexity Score (SCS) surgery utilises procedures such as diaphragm resection and splenectomy to achieve complete macroscopic cytoreduction in patients with higher tumour burden in an effort to improve their survival. [5-9] Nevertheless, preoperative disease burden remains a significant prognostic indicator for survival even after achieving complete cytoreduction.[10] Evidence on outcomes of extensive surgery derives from case-series: no randomised controlled trial directly comparing outcomes from extensive surgery versus low or intermediate complexity surgery for the same pre-operative disease burden has been conducted.[11,12] Meta-analysis of studies have shown survival benefit from maximal cytoreduction [13] but the first population level study investigating the impact of systematic introduction of extensive surgery within a well-defined algorithm of care showed no overall survival benefit, despite doubling complete cytoreduction rate.[14]

OS and PFS are critical outcomes but quality of life (QoL) is important to patients in making treatment decisions.[15,16] Surgical morbidity from extensive surgery is higher[17,18] but comparative evidence on the QoL associated with extensive surgery is lacking.[19] While EORTC 55971, CHORUS, SCORPION and LION trials have published QoL outcomes their results do not report on QoL associated with surgery of varying complexity for similar disease burden.[20]

Understanding QoL after extensive surgery for ovarian cancer is critical given three factors: the absence of randomised controlled trial data comparing extensive surgery versus lower complexity surgery for similar disease burden; the clinical challenge of robust estimation of survival benefit for any individual patient; and the concern that putative survival gain from extensive surgery could be offset by decreased QoL from increased morbidity.[21,22]

A single centre pilot study found that QoL after high SCS procedures for higher disease burden declined postoperatively but recovered within 9 months to levels comparable to that experienced by patients undergoing low or intermediate SCS procedures.[23] The SOCQER-2 study investigated QoL following extensive (high SCS or "ultra-radical") surgery compared to low or intermediate SCS surgery in a prospective observational multi-centre study design. The *a priori* hypothesis, based on the pilot study finding, was that QoL in patients undergoing high SCS surgery would reduce in the short term postoperatively but would recover to levels comparable to that of patients undergoing less complex surgery by 12 months post operation. [24] SOCQER2 was commissioned by the UK National Institute for Health and Care Excellence in order to inform future guidance for ovarian surgery in the UK. [25] The study is reported following STROBE criteria.

Methods

Study design and patient cohorts

SOCQER-2 was a prospective, non-randomised observational study run as parallel studies across the UK, India and Australia. Participating centres aimed to identify and recruit consecutive participants prior to surgical treatment. The recruitment period was September 2015 to September 2016 with follow up until disease progression or death

over 24 months. Ethical approval was obtained (UK Reference number 15/WM/0124), (India reference EC/TMC/68/16).

Patients were eligible if they had suspected or confirmed epithelial ovarian cancer with radiological spread beyond pelvis and if primary (PDS) or delayed debulking surgery (DDS) were planned. Patients receiving neoadjuvant chemotherapy could be recruited prior to chemotherapy or immediately prior to DDS. Patients who did not have FIGO stage III or IV epithelial ovarian cancer on histology following surgery or who did not undergo debulking surgery as planned were subsequently excluded.

Data collected at baseline included Eastern Cooperative Oncology Group (ECOG) Performance Status[26] and modified Age-Adjusted Charlson Comorbidity Index (ACCI). [27] [28] Disease burden was assessed by Peritoneal Carcinomatosis Index (PCI) pre- and post-surgery, and Intra-Operative Disease Mapping (IOM) was used to identify highest level of abdominal disease. [29,30] Surgical data collection captured details of surgeries performed and on intra-and post-operative complications up to 6 weeks which were coded using the Clavien-Dindo classification.[31] The validated Aletti Surgical Complexity Score (SCS) was used define surgical complexity: low (score 1 to 3), intermediate (4 to 7) or high (8 and above). [32] [33,34] Pancreatic tail resection, cholecystectomy, resection from lesser sac and porta-hepatis disease were not included in the original score and were allocated a score of 5: this score modification did not alter the patients' SCS grouping. Data were recorded using the RedCap platform[35] on a secure server.

Quality of life measures

Patients completed validated patient reported outcome measure (PROM) questionnaires EORTC QLQ-30[36] and EORTC OV28, [37] at baseline, or pre-surgery for patients undergoing neoadjuvant chemotherapy, then postoperatively at 6 weeks, 6, 12, 18 and 24 months. [38 39] Patients were offered a choice of postal or online data collection using the secure Q-Tool system. [40] Questionnaire completion ceased on disease progression. Translation of EORTC QLQ OV28 into Bengali was performed in line with EORTC guidelines. [41 42] A change of 5 to 10 points on the EORTC QLC-C30 Global scale was considered small, 10 to 20 points moderate, and greater than 20 large.[15] 10 points was considered clinically meaningful change in line with EORTC55971.[43] We also described the direction of change in the EORTC QLQ-C30 Global scale.[15]

Eligibility/ selection of centres

To ensure that patients undergoing procedures with a range of surgical complexity would be included, high and medium volume gynaecological cancer centres self-declared their practice prior to study participation: some had incorporated high SCS procedures, where appropriate given the patient's disease, into routine practice to varying degrees, others had not. UK gynaecological cancer centres conform to standards set by the Royal College of Obstetricians and Gynaecologists and are staffed by trained subspecialists in gynaecological oncology. Centres in Kolkata, India and Melbourne, Australia were staffed by gynaecological oncologists trained in the UK.

Outcome measures

The primary outcome measure was change in the EORTC QLQ-C30 global score following surgical treatment measured at 6 weeks, 6 months and 12 months post operation; secondary outcomes were EORTC QLQ-C30 dimensional and functional scores and EORTC OV28 at 6 weeks, 6 months and 12 months post operation, and

PFS and OS at 2 years. A complete case general linear repeated measures analysis of variance comparing SCS groups was performed, utilising change from the pre-surgery baseline EORTC QLQ-C30 Global score at 6 weeks, 6 months and 12 months post-surgery with the baseline score fitted as a covariate. Tests for sphericity and fit were carried out. Post hoc comparisons were made using Bonferroni's adjustment. Outcomes were analyzed by SCS groups regardless of whether patients underwent PDS or DDS: this decision was based on trials showing QoL as equivalent in these groups.[20] Further models however included: PDS versus DDS; maximum level of disease; and SCS, PDS versus DDS and maximum level of disease. Data were not considered to be missing at random and there was no data imputation. In line with our hypothesis that differences in QoL between groups would be maximal at 6 weeks and resolved by 12 months, we also compared mean change scores at those time points using all available data. Analysis of subscale outcomes was considered exploratory.

Kaplan Meier survival analysis and Cox proportional hazard regression using a forward stepwise procedure were carried out for Progression free survival (PFS) and Overall Survival (OS) at two years. Progression was as defined by the treating clinician. Variables included in the Cox proportional hazard models were SCS (low, intermediate, high), baseline treatment plan (DDS or PDS), pre-surgical albumin level of <35g/l or >=35g/l, aged >=65 or <65, ACCI of <2 or >=2, highest level of disease and pre-operative PCI (<5, between 6 and 14, or >=15) with likelihood ratio tests of contribution to model determining entry and exit to models at each step. All statistical analysis was conducted in SPSS v24.

Sample size calculation

A sample size calculation was used to identify minimum number needed to detect a clinically meaningful difference between intermediate/low SCS versus high SCS was performed. Assuming that the ratio of group sizes for high SCS to intermediate SCS was 2:1, $\alpha = .05$, power of 80%, a 13 point difference in EORTC QLC-30 of clinical importance and the baseline score was 66 (SD 24) in those undergoing high SCS surgery[42], a sample size of 123 (intermediate =41 and extensive=82) would be required, with additional allowance for dropout (calculations made in Stata 13.1). This was the minimum recruitment target to satisfy the commissioning organization's requirement but recruitment was planned to continue until the end of the one-year period to maximize statistical power to consider confounding factors.

Results

Demographics of recruited cohort

293 patients were recruited from 12 cancer centres in the UK (n=235) and one centre in India (n=58) over a period of 12 months. After surgery and histopathology, 247 (84%) were eligible (Figure 1). Cancer registration data for England indicates that English centres recruited 25% of women with late stage ovarian cancer presenting for surgical resection in the whole recruitment period within their surgical catchment areas, with a range of 10 to 57% at different centres: this range reflects staggered centre set up and in some cases research nurse vacancies. The centre in Australia recruited 13 patients (12 low SCS, 1 intermediate SCS), but PCI scores were not available and so those patients were not considered in the analysis of QoL, as adjustment for disease burden was not possible. More patients in the intermediate and high SCS groups were <65 years, with better performance status and lower co-morbidity measured by the ACCI (Table 1).

Characterisation of disease burden in patient cohort

Pre-operative median PCI was 11 (IQR 13) and 85/247 (34%) had a PCI <= 6, 56/247 (23%) had a PCI 7-12 and 106/247 had a PCI > 12. Low, intermediate, high SCS procedures were performed in 46% (113), 28% (70) and 26% (64) patients respectively. Upper abdominal disease was present in 43% (48), 63% (44) and 92% (59) of patients undergoing low, intermediate or high SCS procedures, respectively p=0.001 (Table 1). Patients undergoing low SCS procedures had PCI and level of disease scores that overlapped with those undergoing intermediate procedures, but those undergoing high SCS had a higher disease burden as defined by higher PCI and more upper abdominal disease, p=0.001 (Table 1, Figure S1).

In the 70% (187) undergoing delayed debulking surgery, 103 (60%) had low, 44 (25%) intermediate and 25 (15%) had high SCS surgery. Among the 30% (75) undergoing PDS, 10 (13%) patients had low SCS, 26 (35%) intermediate SCS and 39 (52%) high SCS (p=0.001). (Table 1). Both patients' pre-operative PCI (Figure S1A) and the complexity of surgery (Figure S1B) varied across participating centres, reflecting differences in surgical ethos. (p=0.001). (Table 1). Pre-operative PCI was lower in women undergoing DDS than in those undergoing PDS (data not shown).

Quality of life

Response rates for patients undergoing intermediate or high complexity surgery groups were >80% of those eligible across all timepoints but were lower for patients undergoing low complexity surgery with 70% responding at 12 – 18 months and 46% at 24 months (Table S1). A minority choose electronic data collection, many of these changing to postal data collection over the course of the study.

Mean change from the pre-surgical baseline in the EORTC QLQ-C30 at 6 weeks post surgery was 3.4 (SD 1.8, n=88) in the low, 4.0 (SD 2.1, n=55) in the intermediate and 4.3 (SD 2.1, n=52) in the high SCS group, p=0.048. At 12 months post surgery the mean change was 4.3 (SD 2.1, n=51) in the low, 5.1 (SD 2.2, n=41) in the intermediate and 5.1 (SD 2.2, n=35) in the high SCS group, p=0.133. (Table 2). In a complete case repeated measures analysis of variance of change from the pre-surgical baseline EORTC QLQ-C30 Global score at 6 weeks, 6 months and 12 months post surgery with the baseline score fitted as a covariate, there were no clinically or statistically meaningful differences in EORTC QLQ-C30 global scores between the three SCS groups, p= 0.840 but there was a small statistically significant improvement over time with patients (p<0.001) (Figure 2). Mean scores allowing comparison to EORTC reference values are given in Table S2. In further models PDS versus DDS and maximum level of disease were not associated with change in EORTC QLQ- C30 Global score.

EORTC QLQ-C30 physical function (p=0.004), role (p=0.001) and emotional function (p=0.016), but not the global score, were lower in high SCS group at 6 weeks post-surgery, but by 12 months there was no difference in physical and emotional function between the three groups (Table S2). In all groups clinically meaningful and statistically significant improvements in physical function was noted at 12 months post operation. There were no differences between the groups with regards to cognitive or social function, both of which improved over time. Intermediate and high SCS groups had higher financial difficulty symptom scores with no other differences in symptom scales both pre- and post- operation (Table S3): this may be related to the younger age profile of these SCS groups. There were no differences in EORTC QLQ-OV28 scores between SCS groups at 12 months post operation (Table S4).

When considering the direction of change in EORTC QLQ-C30 scores from baseline, at 6 weeks post surgery 43 (48.9%) of patients who had undergone low, 23 (41.8%) of those who had undergone intermediate and 19 (35.9%) of those who had undergone high complexity surgery experienced a negative change in EORTC QLQ-C30 global score, while 23 (26.1%), 22 (40%) and 23 (44.2%) respectively experienced a positive change (p=0.219). At 12 months post surgery, 17 (33.1%) of patients who had undergone low, 8 (19.5%) of those who had undergone intermediate and 10 (28.6%) of those who had undergone high complexity surgery had a negative change in EORTC QLQ-C30 global score while 24 (47.1%), 27 (65.9%) and 23 (65.7%) experienced a positive change (p=0.180) (Table S4).

15 out 27 (55.6%) patients with stomas who responded reported a negative change at 6 weeks post surgery, one no change, and eight a positive change in EORTC QLQ-C30 global score compared to 75/179 (41.2%) with no stoma reporting a negative change and 63 reporting a positive change. One patient subsequently had a loop ileostomy following obstruction during chemotherapy. At 12 months post surgery, 9/28 (32.1%) patients with stomas reported a negative change, one no change and eight a positive change in EORTC QLQ-C30 compared to 27/111 (24.3%) with no stoma reporting a negative change and 67 (60.4%) reporting a positive change. There was no difference in the distribution of EORTC QLQ-C30 global score at 6 weeks or 12 months post surgery between those with and without stomas.

Differences in EORTC QLQ-C30 at 18 and 24 months post-surgery were measured with less precision as more of the patients experienced disease progression. At these

time points completion rates from the low SCS group were poorer than intermediate and high SCS groups, suggesting a biased response. (Table S6).

Surgical outcomes

Complete macroscopic tumour clearance was achieved in 56% (63), 71% (50) and 63% (40) of patients undergoing low, intermediate or high SCS procedures respectively, p=0.007 (Table 1). More women in the low SCS group had residual disease, 50/113 (44%), reflecting the presence of upper abdominal disease in 43% of the low SCS group (Table 1).

Liver mobilisation and diaphragmatic peritonectomy or resections were performed in 53 (22%) patients and splenectomy in 21 (9%) patients. Large bowel resection was performed in 60/247 patients, 38 of whom received end colostomy (15%) and 22 primary anastomoses (9%). 30% of patients sustained at least one minor or major post-operative complication (Table S7). Complication rates varied by SCS type (low SCS 20%, intermediate SCS 26%, high SCS 52%, p<0.001). 14.2% had Grade 3 or higher complications, 9% of the low, 13% of the intermediate and 25% of the high SCS patients. Three patients died from complications of surgery: a woman undergoing intermediate SCS developed disseminated intravascular coagulation and multi-organ failure; a woman aged 76 undergoing low SCS died as a result of a pulmonary embolism; and a woman undergoing intermediate SCS with intraoperative blood loss between 2–3 litres developed intra-abdominal sepsis.

Survival

Cumulative PFS at two years was 34% (95% CI 24.7to 42.3%) for low, 47% (95% CI 35.0 to 58.6%) for intermediate and 34% (95% CI 22.4 to 46%) for patients with high

SCS (p=0.109) (Figure S 2A). In forward stepwise Cox regression models that included level of disease, pre-operative PCI, ACCI, residual disease, pre-operative albumin level, age, initial treatment strategy (PDS or DDS) and country, only co-morbidity as measured by the ACCI and upper abdominal disease, and not SCS surgical group, were associated with progression free survival (Table S8). PFS in patients with only pelvic disease was 57% (95% CI 36.8 to 74.4%), in those with mid-abdominal disease 49% (95% CI 37.4% to 61.0%) and was 29% (95% CI 21.4% to 36.0%) in those with upper abdominal disease (p=0.001).

Patients with no residual disease status after the surgery had better PFS (47% vs 21%, p<0.001) and OS (83% vs 64%, p<0.001) at 2 years post operation. There were no differences in PFS or OS according to whether patients received PDS or DDS or by their country of residence and treatment (India or UK, data not included).

Discussion

Main findings

We found that patients with late stage ovarian cancer had no important differences in EORTC QLQ-C30 global scores measured across 6 weeks, 6 months and 12 months post operation when undergoing surgery of varying complexity, despite a higher preoperative disease burden in patients undergoing the most complex surgery. Across all SCS groups, global QoL showed a small but significant improvement by 12 months postoperatively. Patients who underwent the most complex surgery (high SCS group) had small to moderate detriments in EORTC QLQ-C30 physical function, role function and emotional function at 6 weeks post operation compared to patients undergoing less extensive surgery (intermediate and low SCS groups) but by 6-12 months post-surgery these functions are comparable across all SCS categories. A majority of

women undergoing high complexity surgery without disease progression experienced a positive change in quality of life by 12 months post surgery. Our methodologically robust multi-centre study confirms findings from smaller single-centre studies. [24,44]

Those undergoing high SCS procedures had significantly greater disease burden and more upper abdominal disease, but patients with these disease characteristics also underwent surgery of low or intermediate complexity. As some women with comparably high disease burden would not have been offered surgery, understanding the quality of life and survival of these patients not undergoing surgery is essential if the true value or detriment from high SCS surgery is to be assessed. We hypothesise that, where high complexity surgery is not part of routine practice, fewer patients with a high disease burden on imaging pre-operatively will be offered surgery. This interpretation is in keeping with the results from the national ovarian cancer audit from England which demonstrates that only 51% of women with advanced ovarian cancer undergo surgery.[45]

Patients undergoing low complexity surgery had higher rates of residual disease and lower survival compared to those with a similar disease burden undergoing surgery of intermediate complexity. These patients, however, were older with higher comorbidity and lower performance status. The presence of upper abdominal disease and pre-existing comorbidities was associated with poorer progression free and overall survival. Postoperative residual disease was associated with poorer overall survival, particularly in patients undergoing low complexity surgery.

Strengths

Study strengths include a clear a priori hypothesis and a design that addressed patient and disease confounders. This is the first study that investigates quality of life following surgery of different complexity while taking into account disease burden. Centres with differing surgical approaches participated in the study with careful data collection on disease burden and distribution. Validated quality of life instruments were used and production of a validated Bengali translation for EORTC QLQ-OV28 ensured non-English speaking patients in Kolkata were able to participate and that, as far as possible, quality of life assessments were comparable between the Kolkata and the UK centres. There were minimal missing data (>99% data fields complete for clinical and surgical information, 88% PROMs response) and minimal loss to follow-up up to 12 months.

Limitations

Limitations of the study are the cohort design: randomisation would be the gold standard to evaluate survival and quality of life. Given, however, the lack of equipoise amongst surgeons with strong beliefs in the value (or lack of it) of high SCS procedures to achieve complete cytoreduction, a clinical trial would be challenging to deliver. We cannot exclude selection bias, but recruitment to this study was carried out by research nurses, therefore systematic bias introduced by surgeons recruiting patients whom they believed would recover well after extensive surgery is unlikely. Ongoing research by the team will use cancer registration data to investigate bias in the choice of patients for surgical intervention by comparing the recruited patients in each centre to the 'denominator' total patient cohort in each centre.

We recruited fewer women undergoing high and more women undergoing low complexity surgery than we expected at time of sample size calculation, somewhat

reducing our anticipated power regarding outcomes of high SCS surgery. There were, however, no population based data on the proportion and demographics of patients undergoing high complexity procedures from the UK or internationally. A comparative study between two centres in the UK identifies variations in the extent of cytoreductive surgery. [46] On a larger scale, results from the population based national ovarian cancer audit in England has demonstrated significant geographical variation in rates of surgery [45] . Similarly, registry data from the Netherlands shows significant variation in the proportion undergoing complete cytoreductive surgery, [47] while in the USA, only 48% of ovarian cancer surgery is guideline compliant.[46] These papers confirm that the true utilisation of extensive surgery/high SCS procedures on a population basis in the 'real world', as opposed to that reported in academic publications from selected centres, is simply not known. Furthermore, publications on outcomes from high SCS surgery rarely present total cohort 'denominator' data.[14,22]

Interpretation in light of other evidence

Maximal effort cytoreductive surgery has been shown in studies to improve survival from advanced ovarian cancer. Evidence on quality of life in patients undergoing extensive/high complexity compared to lower complexity surgery for similar disease burden is scarce. Our study shows that quality of life improved over 12 months compared to preoperative scores in the majority of patients undergoing low/intermediate or high SCS procedures. High complexity cytoreductive surgery did not result in poorer quality of life compared to intermediate or low complexity procedures. There were no clinically meaningful differences in QoL between patients undergoing surgery of different complexity.

Recommendation for practice

Patients undergoing high complexity surgery can be reassured that by 12 months post operation, most will have better quality of life before than immediately before surgery.

Research recommendation

Our findings on variation in practice, surgical ethos, distribution of disease burden in surgeries of different complexity and outcomes are novel but highly likely to be generalisable across health systems. Research is needed to understand the reasons for this variation in surgical approach, its relationship with survival outcomes and algorithms that can improve standardisation of surgical decision making.

Conclusions There can be confidence in clinical practice that the use of high complexity surgery in advanced ovarian cancer will not have a significant or clinically meaningful detrimental effect on global quality of life compared to less complex surgery. Short term impacts on physical function, emotional and role domains need to be discussed with patients and appropriate support provided to women undergoing extensive surgery.

Funding

SOCQER2 study in the UK was commissioned and funded by the National Institute of Health and Care excellence. The funder had no role in interpretation of results from the study. The SOCQERoOZ study, conducted at Royal Women's Hospital and Peter

MacCallum Cancer Centre in Melbourne, received research grant from Australian Society of Gynaecologic Oncologists Inc. The SOCQER2 India study is part funded by the Department of Science Technology, India - UKIERI grant and Jiv Daya Foundation, USA.

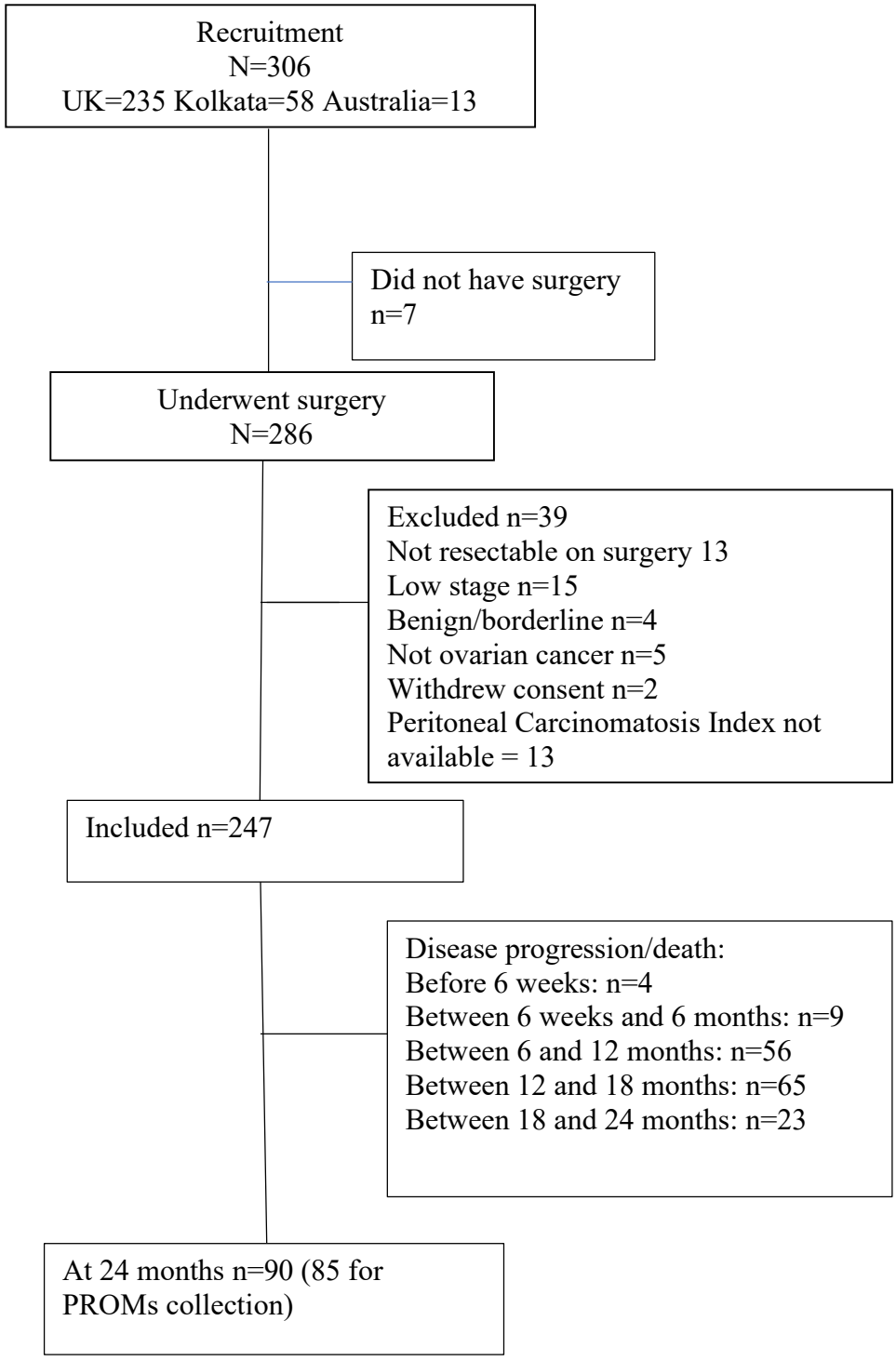
Author contributions

SS and CC secured funding, designed and conducted the study. SK, JL conducted the study, collected the data and SK, JL and CC analysed results from the study. All co-authors contributed intellectually to the design of the study, contributed clinical data and interpreted the results of the study for clinical practice. All authors reviewed the manuscript prior to submission. Authorship order for all authors apart from the study team at Birmingham is based in alphabetical order.

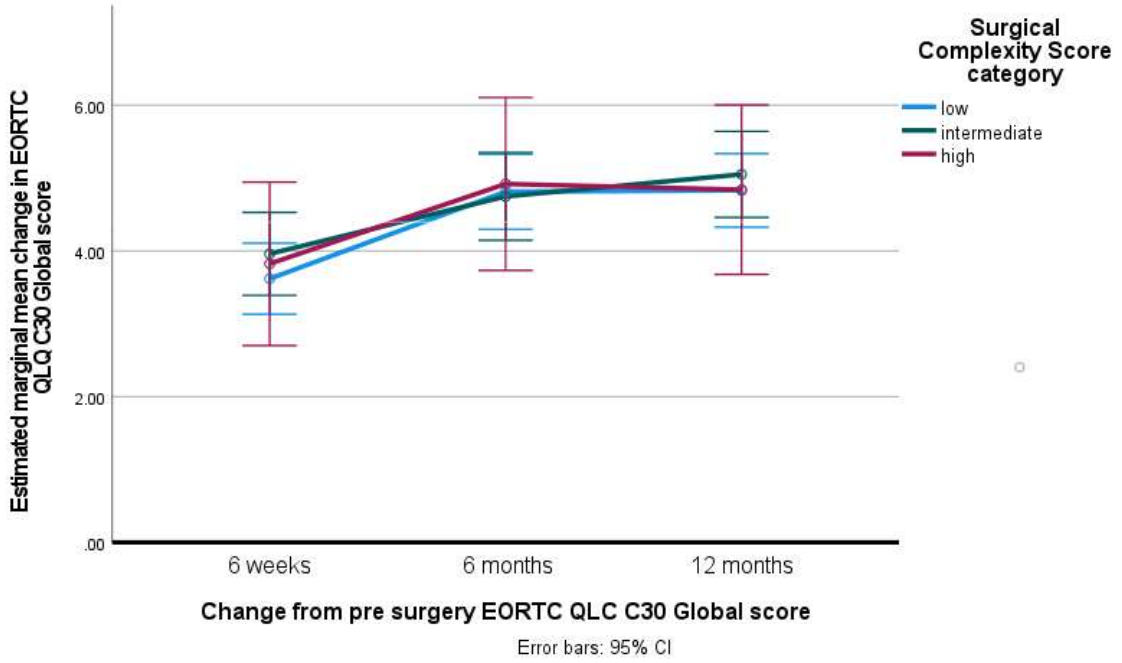
Disclosures

SS has received honoraria from Astra Zeneca, MSD and GSK outside the submitted work. CF has received honoraria from Ethicon, Tesaro, MSD/Astra Zeneca, Clovis, Roche, GSK. RM reports grants from Barts Charity, grants from The Eve Appeal, personal fees from Astra Zeneca, MSD, outside the submitted work. RE reports personal fees from Astra Zeneca, personal fees from Clovis Pharma, personal fees from GSK, outside the submitted work.

Figure 1: Study flow diagram



493 **Figure 2: Change in EORTC QLQ-C30 Global score from surgical baseline by surgical complexity**



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495 **Table 1: Baseline and postoperative patient characteristics by modified Aletti Surgical Complexity Score group**

Patient characteristics	Low SCS N=113		Intermediate SCS N=70		High SCS N=64		
	Number	%	Number	%	Number	%	p value
Age in 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	
ECOG 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 kg/m2							
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							
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 (Highest level of disease - pelvis)	20	17.7	7	10	0	0	0.001
Level 2 (Highest level of disease - mid-abdomen)	45	39.8	19	27.1	5	7.8	
Level 3 (Highest level of disease - upper abdomen)	48	42.5	44	62.9	59	92.2	
Outcome of surgery: residual disease							
None visible	63	55.8	50	71.4	40	62.5	0.007
< 1 cm	29	25.7	17	24.3	21	32.8	
<=1 cm	21	18.6	3	4.3	3	4.7	
Final FIGO stage							
3A/3B	11	9.7	9	12.9	2	3.1	0.068
3C	68	60.2	34	48.6	33	51.6	
4	31	27.4	26	37.1	29	45.3	
Post-operative chemotherapy							
Carboplatin+/- Taxol	106	94	62	89	62	97	0.591
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 EORTC QLC30 Global (Mean (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	5	3	6	3	9	8	0.001
Surgery to chemotherapy interval	31	16	31	13	39	20	0.005

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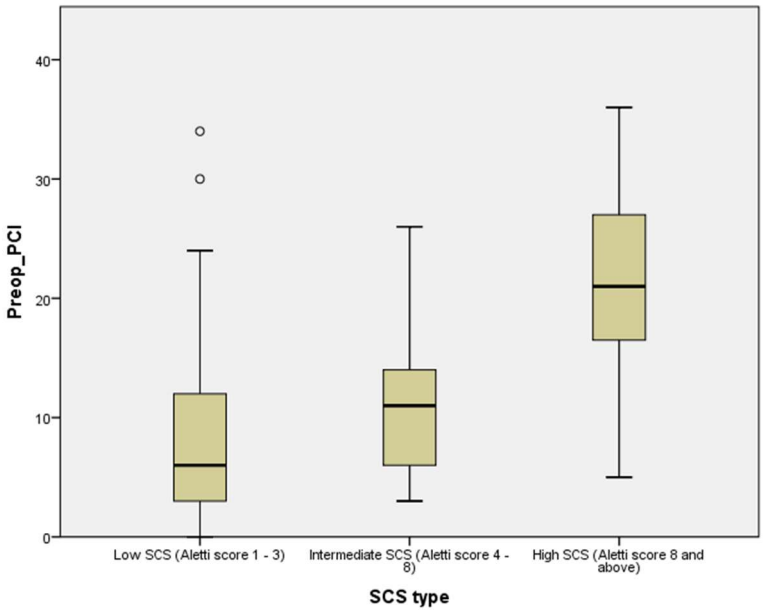
Table 2: Estimated mean change in EORTC QLQ-C30 Global scores by SCS group with pre-surgery score as a covariate

	6 weeks post-surgery			6 months post-surgery			12 months post-surgery		
SCS score	Estimated mean	95% confidence interval		Estimated mean	95% confidence interval		Estimated mean	95% confidence interval	
Low	-2.9	-8.1	2.3	8.5	2.9	14.1	7.5	1.9	13.2
Intermediate	-1.4	-7.1	4.4	8.9	2.7	15.0	8.4	2.2	14.7
High	-0.1	-6.7	6.5	2.9	-4.1	10.0	7.1	1.0	14.2

Figure S1: Distribution of Peritoneal carcinomatosis by Surgical complexity score type amongst recruited patients in study

S1B: Distribution of pre-operative PCI by SCS group



S1B: Distribution of pre-operative PCI by participating centres

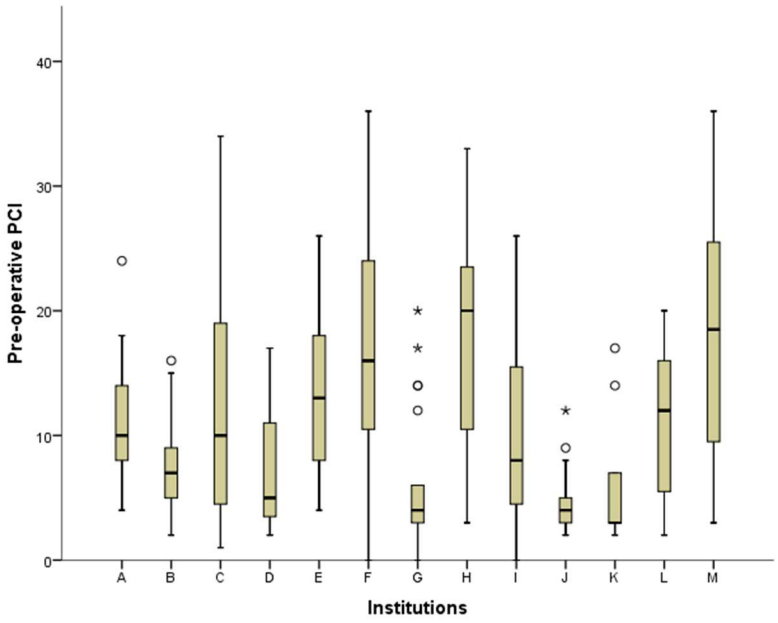
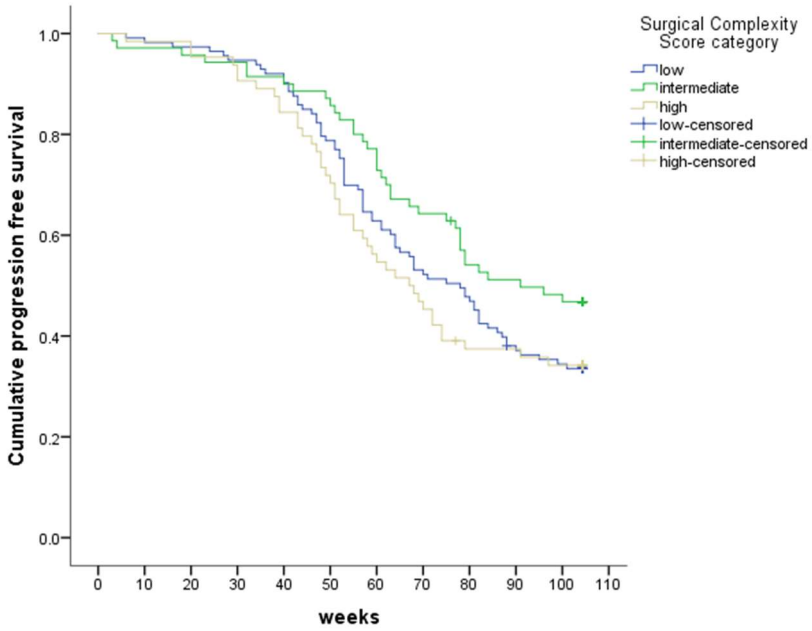


Figure S2A: Cumulative progression free survival by SCS type up to 2 years



S 2B: Cumulative overall survival by SCS type up to 2 years

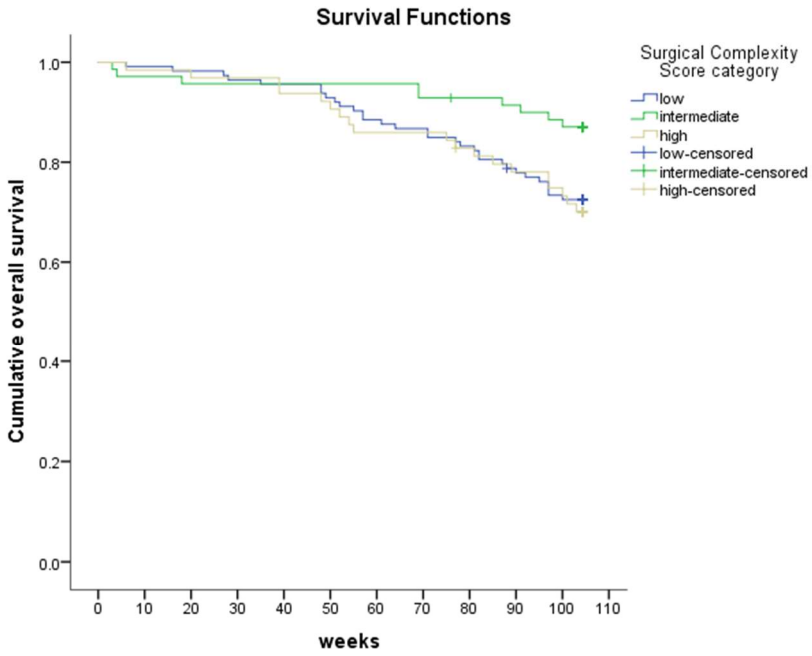


Table S1: Patient reported outcome measures (PROMs) completion rate and loss to follow-up

Time points	PROMs data completed	PROMs data expected (n=247)	Percentage of PROMs data completed	Reasons for change in eligible participants at each time point – cumulative numbers
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

Table S2: EORTC QLQ-C30 in patients by Surgical Complexity Score group

EORTC QLQ C30	Types of surgery	Pre-surgery			6 weeks			6 months			12 months			p value*
		N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Global QoL	Low	98	65.1	21.7	98	59.9	19.5	93	69.9	19.8	57	72.2	20.5	**<0.001
	Intermediate SCS	62	59.8	19.9	61	60.1	19.3	53	67.3	21.5	44	74.4	18.6	***0.539
	High	59	58.1	22.2	56	60.1	18.9	52	66.5	20.1	38	73.5	16.9	
	p					0.986#						0.867#		
Functional QoL: Physical function	Low	99	75.7	19.8	97	64.5	20.2	93	76.3	21.5	56	80.6	18.9	**<0.00
	Intermediate SCS	60	74.0	23.1	59	67.8	18.0	54	73.2	17.6	45	77.9	20.8	***0.009
	High SCS	60	73.4	20.9	50	55.6	18.6	54	64.4	24.2	40	76.5	19.3	
	P					0.004#			0.007#			0.528#		
Functional QoL: Role function	Low	99	66.5	29.0	99	45.1	27.5	94	70.7	27.4	57	80.1	25.1	**<0.001
	Intermediate SCS	61	65.8	28.8	60	52.8	26.8	55	67.9	29.7	45	75.2	24.8	***0.070
	High	59	64.7	27.9	57	39.2	23.9	56	60.7	33.7	40	69.6	29.5	
	p					0.016#						0.166#		
Functional QoL: Emotional function	Low	98	78.1	21.1	98	76.8	21.4	93	79.7	20.6	56	78.6	22.2	**0.430
	Intermediateee SCS	62	63.7	27.2	61	72.4	20.8	55	75.8	19.7	44	75.4	19.0	***0.005
	High	59	62.6	25.4	57	69.3	19.4	55	69.2	25.7	39	73.3	23.4	
	p					0.034#			0.036#			0.548#		
Functional QoL: Cognitive function	Low	99	78.3	21.2	99	75.9	21.1	91	78.2	21.3	56	81.3	20.1	**0.732
	Intermediate SCS	62	76.3	26.2	61	78.1	21.2	55	78.2	20.8	45	79.3	24.9	***0.731
	High	60	76.7	24.0	57	76.0	19.	56	76.5	25.0	40	81.7	22.6	
	p					0.672#						0.820#		
Functional QoL: Social function	Low	98	65.1	29.4	98	58.8	28.1	93	74.9	26.1	56	84.5	22.2	**<0.00
	Intermediate SCS	61	58.7	29.9	59	60.5	26.2	55	71.5	31.5	45	83.0	21.8	**0.213
	High	60	63.6	29.2	57	57.0	29.9	56	64.6	30.3	39	79.5	23.1	
	p					0.850#						0.481#		

*complete case general linear repeated measures (one way ANOVA) at 12 months ** within group change across 6 weeks, 6 months and 12 months
*** between SCS group change
# Kruskal-Wallis test all available data at that time point

Table S3: EORTC QLQ-C30: Symptoms scales by Surgical Complexity Score group

Symptom scale	Types of surgery	Pre-surgery			6 weeks			6 months			12 months			p value
		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	*<0.001
	Intermediate SCS	61	38.1	22.2	61	42.4	21.8	55	39.6	24.2	45	30.6	22.2	**0.798
	High SCS	60	36.5	21.5	57	49.1	21.3	56	40.7	27.8	40	26.7	20.9	
	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	*0.030
	Intermediate SCS	59	14.7	24.4	60	13.9	19.2	55	11.5	23.1	45	10.7	21.4	**0.336
	High SCS	59	11.6	15.2	57	15.5	21.3	56	11.6	23.1	40	7.5	13.6	
	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	*<0.001
	Intermediate SCS	61	26.2	27.1	61	28.1	24.4	55	28.5	27.0	45	22.2	26.1	**0.772
	High SCS	60	23.9	23.6	57	29.8	22.7	56	26.5	28.4	40	14.2	18.3	
	p				0.600#						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	*0.468
	Intermediate SCS	61	15.8	25.5	61	16.4	23.3	54	22.8	30.9	45	13.3	25.0	**0.837
	High SCS	60	17.8	20.8	57	18.1	27.5	56	17.9	23.8	40	15.8	21.3	
	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	*0.007
	Intermediate SCS	61	36.1	31.8	58	39.7	33.9	54	35.2	31.3	45	27.4	27.8	**0.812
	High SCS	60	35.6	32.4	57	36.3	31.7	56	32.7	32.7	40	25.8	29.7	
	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	*<0.001
	Intermediate SCS	61	31.1	32.7	61	25.7	28.8	55	13.9	24.6	45	10.4	22.3	**0.208
	High SCS	60	31.7	31.5	57	33.9	32.4	56	23.8	31.6	40	7.5	19.2	
	p				0.240#						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	*<0.001
	Intermediate SCS	61	24.0	29.3	61	37.7	33.6	55	21.8	30.2	45	16.3	25.2	**0.556
	High SCS	59	26.0	31.6	57	35.7	33.8	56	23.2	33.6	40	17.5	26.1	
	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	*0.079
	Intermediate SCS	62	11.3	23.3	61	13.1	23.0	55	12.1	23.5	45	7.4	15.7	**0.204
	High SCS	59	10.2	21.7	57	17.5	26.8	55	12.7	20.8	40	13.3	25.9	
	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	*0.103
	Intermediate SCS	62	31.2	35.6	60	24.4	34.1	55	27.3	35.2	44	18.2	26.4	**0.002
	High SCS	59	21.5	33.8	57	26.3	35.5	56	21.4	32.7	40	22.5	29.6	
	p				0.062#						0.005#			

* within group change across 6 weeks, 6 months and 12 months ** between SCS group change # Kruskal-Wallis test all available data at that time point

Table S4: EORTC QLQ-OV28 symptom scales by SCS group

EORTC QLQ OV28 Symptom scale	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	
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
	Intermediate. 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				0.820#						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
	Intermediate. 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#						0.610#									
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
	Intermediate. 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
	Intermediate. 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
	Intermediate. 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
	Intermediate. 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
	Intermediate. 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	
	p				0.010#						0.482#									

* within group change across 6 weeks, 6 months and 12 months ** between SCS group change # Kruskal-Wallis test all available data at that time point

Table S5: Direction of change in EORTC QLQ-C30 Global score from pre surgery baseline at 6 weeks and 12 monhts post operation

Change in EORTC QLQ-C30 Global score from pre surgery baseline	Surgical Complexity Score					
	low		intermediate		high	
	Count	%	Count	%	Count	%
6 weeks post surgery:						
Any negative change	43	48.9	23	41.8	19	43.6
large negative change	*18*	*20.5*	*9*	*16.4*	*8*	*15.4*
moderate negative change	*13*	*14.8*	*9*	*16.4*	*7*	*13.5*
a little negative change	*12*	*13.6*	*5*	*9.1*	*7*	*7.7*
No change	22	25.0	10	18.2	10	19.2
Any positive change	23	26.1	22	40.0	23	44.2
a little positive change	*8*	*9.1*	*1*	*1.8*	*1*	*3.8*
moderate positive change	*11*	*12.5*	*14*	*25.5*	*12*	*19.2*
large positive change	*4*	*4.5*	*7*	*12.7*	*12*	*21.2*
Total	88		55		52	
12 months post surgery:						
Any negative change	17	33.3	8	19.5	10	28.6
large negative change	*8*	*15.7*	*5*	*12.2*	*5*	*14.3*
moderate negative change	*3*	*5.9*	*3*	*7.3*	*1*	*2.9*
a little negative change	*6*	*11.8*	*0*	*0.0*	*4*	*11.4*
No change	10	19.6	6	14.6	2	5.7
Any positive change	24	47.1	27	65.9	23	65.7
a little positive change	*5*	*9.8*	*2*	*4.9*	*1*	*2.9%*
moderate positive change	*9*	*17.6*	*9*	*22.0*	*8*	*22.9%*
large positive change	*10*	*19.6*	*16*	*39.0*	*14*	*40.0%*
Total	51		41		35	

Table S6: EORTC QLC-C30 scores at 18 months and 24 months

EORTC QLQ-C30		18 months			1.	24 months			
		N	Median		IQR	N	Median	IQR	
Global	Low SCS	39	75.00	66.67	83.33	20	75	58.33	83.33
	Intermediate SCS	32	83.33	66.67	83.33	20	83.33	66.67	87.50
	High SCS	29	66.67	50.00	83.33	16	70.83	50.00	83.33
Kruskal-Wallis test		p=0.022				p=0.416			
Physical function*	Low SCS	39	86.67	66.67	93.33	20	86.67	63.33	96.67
	Intermediate SCS	32	90.00	76.67	93.33	22	86.67	80.00	100.00
	High SCS	31	80.00	66.67	93.33	19	93.33	80.00	100.00
Role function*	Low SCS	39	100.00	66.67	100.00	20	100	50.00	100
	Intermediate SCS	33	100.00	66.67	100.00	22	100	83.33	100
	High SCS	31	66.67	50	100.00	19	83.33	50.00	100
Emotional function*	Low SCS	39	75.00	66.67	100.00	20	79.17	62.50	100
	Intermediate SCS	33	83.33	75.00	100.00	22	83.33	75.00	100
	High SCS	31	75.00	50.00	83.33	19	75.00	50.00	91.67
Cognitive function*	Low SCS	39	83.33	66.67	100.00	20	83.33	66.67	91.67
	Intermediate SCS	33	83.33	83.33	100.00	22	83.33	83.33	100.00
	High SCS	31	83.33	66.67	100.00	19	83.33	66.67	100.00
Social function*	Low SCS	39	100.00	66.67	100.00	20	100	75.00	100.00
	Intermediate SCS	33	100.00	83.33	100.00	21	100	66.67	100.00
	High SCS	31	83.33	50.00	100.00	18	58.33	50.00	100.00

* Kruskal Wallis test not statistically significant for all functional scales at 18 and 24 months

Table S7 : Intra-operative and post operative complications by SCS

	Intra-operative complications						Post-operative complication	
SCS type	**Haemorrhage**	**Urinary tract injury**	**GI injury**	**Vascular injury**	**Anaesthetic complications**	**Total, n (%)**	**C-D class 2, conservative management n (%)**	**C-D class Radiologi surgical managem without G n (%)**
Low (n=113)	0	2	2	1	2	7 (6.2)	12	9
Intermediate (n=70)	0	2	1	2	1	6 (8.6)	9	6
High (n=64)	1	1	2	2	1	7 (10.9)	17	9
Total (n=247)	1	5	5	5	4	20 (8.1)	38 (15.4)	24 (9.7)

Table S8: Progression free and overall survival adjusted hazard ratios up to two years

a) Progression free survival

	Hazard ratio (Exp(b))	95.0% CI	
ACCI >2	1.62	1.18	2.23
Pelvic disease only and (reference)	1		
Pelvic and mid abdominal disease	1.34	0.69	2.58
Upper abdominal and other disease	2.34	1.29	4.26

b) Overall survival

	Hazard ratio (Exp(b))	95.0% CI	
Intermediate SCS (reference)	1		
Low SCS	2.56	1.19	5.50
High SCS	1.68	0.73	3.88
ACCI > 2	2.08	1.21	3.59
Pre-operative albumin <35g/l	2.00	1.14	3.50
Pre-operative PCI ≤5 (reference)	1		
Pre-operative PCI 6-14	2.18	0.99	4.79
Pre-operative PCI≥15	3.80	1.67	8.64

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