Quality of life after early enteral feeding versus standard care for proven or suspected advanced epithelial ovarian cancer: results from a randomised trial

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Running Head: enteral feeding and ovarian cancer surgery outcomes

ABSTRACT

Background: Malnutrition is common in patients with advanced Epithelial Ovarian Cancer (EOC), and is associated with impaired quality of life (QoL), longer hospital stay and higher risk of treatment-related adverse events. This phase III multi-centre randomised clinical trial tested early enteral feeding versus standard care on postoperative QoL.

Methods: From 2009-2013, 109 patients requiring surgery for suspected advanced EOC, moderately to severely malnourished were enrolled at five sites across Queensland and randomised to intervention (n=53) or control (n=56) groups. Intervention involved intraoperative nasojejunal tube placement and enteral feeding until adequate oral intake could be maintained. Despite being randomised to intervention, 20 patients did not receive feeds (13 did not receive the feeding tube; 7 had it removed early). Control involved postoperative diet as tolerated. QoL was measured at baseline, 6 weeks postoperatively and 30 days after the third cycle of chemotherapy. The primary outcome measure was difference in QoL between intervention and control group. Secondary endpoints included treatment-related adverse event occurrence, length of stay, postoperative services use, and nutritional status.

Results: Baseline characteristics were comparable between treatment groups. No significant difference in QoL was found between the groups at any timepoint. There was a trend towards better nutritional status in patients who received the intervention but the differences did not reach statistical significance except for the intention-to-treat analysis at 7 days postoperatively (11.8 intervention vs. 13.8 control, p 0.04).

Conclusion: Early enteral feeding did not significantly improve patients' QoL compared to standard of care but may improve nutritional status.

Funding: Cancer Australia project grant 631524

INTRODUCTION

Epithelial Ovarian Cancer (EOC) represents approximately 90% of all malignant ovarian tumours and is associated with a worse prognosis compared to other gynecologic malignancies [1]. World-wide,

53 an estimated 238,719 women were diagnosed with, and 151,917 died from ovarian cancer in 2012
54 [2, 3]. Similar to the United States, ovarian cancer has the sixth highest mortality rate of all cancers
55 in women in Australia after cancers of the lung, breast, colon, pancreas and unknown primary site,
56 and supportive care treatments to improve survival are urgently needed [4, 5].
57 The location of ovarian tumours deep within the pelvis and abdomen, along with usually nonspecific
58 symptoms and ineffective screening makes early diagnosis difficult, thus patients tend to present
59 late with advanced stages of EOC (III and IV) [1, 6]. Treatment typically involves a combination of
60 extensive cytoreductive surgery and intensive chemotherapy for several months [1]. The treatment
61 results in considerable physical, psychological, social and economic impacts [1].
62 Abdominal bloating, tumour load, ascites, pleural effusions and even subclinical bowel obstruction
63 are associated with the presence of advanced EOC and reduce the patient's ability to eat, leading to
64 worsening nutritional status [1, 6]. Ovarian cancer patients have a 19-times higher odds to be
65 malnourished at diagnosis compared with patients with benign gynaecological disease [7].
66 Malnutrition is also associated with impaired quality of life (QoL) and longer hospital stay, as well as
67 higher risk of treatment-related adverse events following surgery [6, 8].
68 Among patients with various types of gynaecological cancer, several studies have shown early oral
69 diet to be associated with reduced length of hospital stay, reduced postoperative discomfort and
70 faster resolution of postoperative ileus following surgery [6]. However, many patients may not
71 achieve an adequate intake for the first few days after surgery, and for a patient who enters surgery
72 in a malnourished state this may increase their likelihood of worse treatment outcomes and reduced
73 QoL. In patients treated for other cancers where malnutrition is an issue, enteral feeding has been
74 tested and found to be beneficial [9-15].
75 These studies have been performed mainly in patients with gastrointestinal and lung malignancies,
76 as well as in patients undergoing radiotherapy for head and neck cancers [9-15]. They consistently
77 reported improved outcomes of the nutritional interventions including a reduction in postoperative
78 complications [9, 10, 16], a shorter length of hospital stay [9, 10, 13], an improvement in protein

metabolism [13], or reduction in weight loss [15] and some concluded that it is cost-effective to support patients with enteral feeding [12, 13, 17]. Compared to standard care, which means oral diet as tolerated, studies have found a nutritional benefit of enteral feeding in adult patients with colorectal and gastric cancer, and paediatric patients with brain tumours, myeloid leukaemia or high-risk solid tumours [18-20]. These patients receiving enteral feeding were found to have significantly better nutritional status and immune function, and accelerated recovery following surgery [18, 19].

Enteral feeding may improve epithelial structure and function [21, 22], enhance mucosal immunity [23], and reduce the risk of bacterial translocation. In patients with functioning gastrointestinal tracts, enteral feeding is preferred for nutritional support over the parenteral route due to lower risk of infections, lower costs, and shorter length of stay in hospital [9, 10, 24].

However, there is a lack of studies examining the effects of enteral feeding after surgery on outcomes specifically for EOC patients. Enteral feeding has been proposed as the preferred way to deliver caloric intake, because it is less invasive than total parenteral nutrition and its complication rates are lower [9, 10].

We report findings from a prospective, randomised, multi-centre clinical trial investigating whether early postoperative enteral nutrition for malnourished women with advanced EOC can improve their QoL, nutritional status, perioperative and postoperative outcomes compared to control.

METHODS

Ethical approval

All relevant hospital and university human research ethics committees approved this trial. The OPEN trial is registered with ClinicalTrials.gov, number NCT00850772.

Participants

Participants were enrolled through one of five participating sites in Queensland, Australia, and were eligible for inclusion if they required planned upfront or interval cytoreductive surgery for suspected

or proven advanced EOC, primary peritoneal cancer or fallopian tube cancer; had signs of moderate or severe malnutrition defined as Patient-Generated Subjective Global Assessment (PG-SGA) category B or C; were medically fit for cytoreductive surgery; signed a written informed consent; and were females aged 18 years or older. Participants were excluded if they had other cancers, or recurrent EOC; if they had contraindications to enteral feeding such as ileus, gastrointestinal ischaemia, bilious or persistent vomiting, or mechanical obstruction; if they had a positive urine pregnancy test; or if they were unfit for surgery, at the discretion of the investigator.

Randomisation and masking

Randomisation was performed centrally, after stratification by treatment site and mode (upfront surgery vs. neoadjuvant chemotherapy). Masking was not possible due to the nature of the treatment; sham treatment was not used due to ethical concerns.

Procedures

All patients completed a PG-SGA questionnaire to assess their nutritional status. Patients meeting the inclusion criteria for the study were asked for written informed consent to participate in the study.

Enrolled participants were asked to complete the baseline QoL assessment and a demographic questionnaire. All participants underwent medical imaging of the pelvis, abdomen and chest for staging, had a serum biochemistry including serum albumin, full blood count, serum tumour markers (CA 125, CA 19.9, CEA) taken and also received a 12-lead electrocardiogram as per routine preoperative work-up. At baseline, participants received a physical examination, weight and height measurements.

The intervention group underwent insertion of a soft, fine-bore nasojejunal tube inserted by the anaesthetist during surgery, through the participant's nostrils and forwarded into the proximal small bowel. The tubes were fitted with a guide wire and a weighted tip. The location of the nasojejunal tubes was checked by the surgeon via manual palpation intraoperatively and was confirmed by plain X-ray postoperatively prior to the commencement of feeding. Iso-osmolar feeds, continuous over 24

hours were used for postoperative feeding. A standard fibre-containing, high-protein enteral nutrition formula (4.2 kJ/mL or 1 kcal/mL) was fed through the nasojejunal tube postoperatively. This standard feed contains 20% protein, 30% fat and 50% carbohydrate. Feeding was commenced at a rate of 40ml/hr at 4 hours for the first 24 hours. Then, feed rates were increased to provide participants nutrition of 125 kJ/kg body weight, adjusted using standard methodology for overweight patients. Participants randomised to this group were monitored daily by a nutritionist and had their diet modified according to these assessments. Enteral feeding was ceased once the participant was able to maintain an adequate oral intake, defined as 65-75% of the daily nutritional requirements.

Study endpoints

QoL questionnaires were completed by participants at baseline, 6 weeks postoperatively and 30 days following completion of the third cycle of chemotherapy. QoL was measured using the Functional Assessment of Cancer Therapy-General (FACT-G, range 0-108) questionnaire [25, 26]. In combination with the FACT-G questionnaire, an additional 12-item ovarian subscale forms the Functional Assessment of Cancer Therapy-Ovarian (FACT-O, range 0-156) and this was used to measure QoL specific to issues concerning ovarian cancer patients[27]. Better QoL is indicated by higher scores on subscale and summary scores. Health utility was assessed using EQ5D Index and EQ5D visual analogue scale (VAS)[28]. Participants also completed the Hospital Anxiety and Depression Scale (HADS)[29].

Nutritional status and pain were monitored at baseline, 1 and 6 weeks postoperatively and 30 days following completion of the third cycle of chemotherapy by completing the PG-SGA. Weight, body mass index (BMI) and Eastern Cooperative Oncology Group (ECOG) performance score were measured at baseline, 6 weeks postoperatively and 30 days following completion of chemotherapy. Protein and energy intake was recorded at baseline, 7 days, 14 days, and 6 weeks postoperatively and at 30 days following completion of the third cycle of chemotherapy.

Information on medical and surgical history, concomitant illnesses measured by Common Toxicity Criteria version 3 (CTC v3) and all medications used currently and within the past 12 months were extracted from the medical records. Adverse events (AEs) were recorded from baseline until 30 days after completion of chemotherapy according to Common Terminology Criteria for Adverse Events version 3.0 (CTC-AE v3.0).

Further data included total length of hospital stay, whether each participant was admitted to the intensive care unit (ICU) or high dependency unit (HDU), and if so, the length of stay (LOS) in ICU or HDU. At 7 and 14 days postoperatively, a record was made of whether or not participants had nausea or vomiting, or had required a blood transfusion.

Statistical analysis

Statistical analyses were performed using SAS 9.3. Intention-to-treat analyses were performed. For each outcome examined, distribution was assessed visually for normality using histograms and QQ-plots. For continuous normal distributions including raw scores and changes from baseline, T-tests were performed to compare treatment arms. For non-normal or skewed continuous outcomes including raw scores and changes from baseline, Wilcoxon rank-sum tests were performed. Categorical outcomes were compared between treatment arms using Chi-squared tests of homogeneity.

T-tests were performed to compare QoL measures, FACT-G, FACT-O, weight, BMI, ECOG, EQ5D index, and EQ5D VAS Health score between arms at the predefined timepoints.

Wilcoxon tests were performed to compare PG-SGA, pain score, protein, energy, and length of hospital stay between arms.

Chi-squared tests of homogeneity were performed to compare the categorical outcomes including HADS anxiety and depression level categories, PG-SGA Global categories, proportion admitted to ICU or HDU, proportion with postoperative nausea or vomiting, proportion requiring blood transfusions and frequency of AE occurrence, both inclusive and exclusive of AEs thought to be unrelated to

intervention. Comparisons between arms were conducted at baseline, perioperatively, at 7 days, 14 days and 6 weeks postoperatively, and at 30 days post-chemotherapy.

The same tests described above were used to compare outcomes in as-treated analyses, comparing patients who actually received the intervention (N=33) against those who did not (N=76). This study is registered with ClinicalTrials.gov, number NCT00850772.

Role of the funding source

The study sponsors had no role in study design, collection, analysis, or interpretation of data, or writing of the report. The corresponding author had full access to all of the data and the fi nal responsibility to submit for publication.

RESULTS

Overall, 690 patients were assessed for eligibility; 483 patients did not meet the eligibility criteria, 67 declined to participate and 31 were not enrolled for other reasons, but 109 participants met eligibility criteria and were enrolled across the 5 sites between February 2009 and March 2013 (Consort diagram, Figure 1). Of these, 53 were randomly allocated to the intervention, and 56 to the control group. While all patients fulfilled the eligibility criteria, 13 patients (8 control, 5 intervention) had no evidence of malignancy and 7 patients (3 control, 4 intervention) had a borderline tumour. Those 20 patients (18%) presented with large pelvic masses, ascites and elevated serum tumour marker CA125 and were considered “suspicious” for EOC. Overall, 34 patients (31%) received neoadjuvant chemotherapy prior to surgical cytoreduction and 81 (74%) received adjuvant chemotherapy, excluding patients in which the diagnosis of ovarian cancer was not confirmed and a benign or ovarian borderline tumour was diagnosed on subsequent histopathology.

Women assigned to intervention or control groups were comparable at baseline in terms of demographic and clinical characteristics (Table 1). Mean age of participants was 62 years (range 37-85) in the intervention and 64 (range 31-84) years in the control arm at randomisation. Overall, 29% of the intervention and 22% of the control arm had private health insurance, and 49% of the

intervention and 48% of the control group were retired. ECOG performance status was 2 or more in 30% of the intervention and 32% of the control group.

Despite being randomised to the intervention group, 20/53 (38%) participants did not receive feeds via the nasojejunal tube. Thirteen patients did not receive a tube. Reasons included extensive disease preventing nasojejunal tube placement (n=8), forgetting to insert tube (n=3), participant refusal of tube insertion (n=1), and cancellation of surgery in favour of palliative treatment (n=1). Seven patients had early tube removal and did not receive feeds.

Therefore, both intention-to-treat and as-treated analyses were performed to estimate the effect of the intervention.

For the intention-to-treat analysis, there was evidence that patients in the intervention group had better nutritional status, as measured by mean PG-SGA Score, at 7 days postoperatively (11.8 intervention vs 13.8 control group, p 0.04). The as-treated analysis showed better nutritional status for those receiving enteral nutrition but this did not reach statistical significance (11.8 vs 13.3 as-treated analysis, p 0.21). Beyond the first week after surgery, there was a consistent trend towards better PG-SGA score in the intervention group, but the differences did not reach statistical significance (Table 2).

No significant differences were found between treatment arms in QoL measures in terms of raw scores or change from baseline scores in either intention-to-treat or as-treated analyses. Results from intention-to-treat analysis are reported in Table 3. In both treatment arms, mean QoL had improved by 6 weeks postoperatively as measured by FACT-G, FACT-O, EQ5D index and Euroqol-VAS, and this improvement was similar between groups. The mean for these QoL measures had improved even further for both treatment groups at the chemotherapy follow-up (Table 3). No significant difference was found between treatment arms in length of hospital stay (Figure 2).

In both intention-to-treat and as-treated analyses, no significant differences were found between treatment arms in pain score, adverse event occurrence, protein and energy intake, weight, ECOG, proportion admitted to ICU or HDU, proportion with nausea/vomiting or proportion requiring blood

transfusion. These clinical outcomes at 7 days postoperatively are summarised in Table 3. There was no significant difference between arms in postoperative mortality, with one death among participants in the control group and no deaths within the intervention arm within 30 days of surgery.

DISCUSSION

In patients with advanced EOC suffering from moderate to severe malnutrition early enteral feeding through a nasojejunal tube may be associated with improved postoperative nutritional status 7 days after surgery. However, the effect was statistically not significant in the as-treated analyses possibly due to the small number of patients who received feeds. Early enteral feeding left QoL and surgical outcomes unchanged.

While the benefits of nutritional interventions are widely accepted for patients with several other types of cancer types [9-15], the evidence for postoperative enteral feeding in ovarian cancer is sparse. The best documented research effort has been described by Spirtos and Ballon who conducted a prospective, randomised trial on early enteral feeding of gynaecological cancer patients via needle catheter jejunostomy. A total of sixty patients were randomised, of which 29 patients had EOC and only 16 patients received the intervention and only a quarter of all patients randomised were actually malnourished. The authors concluded that postoperative nutrition was maintained effectively with few complications [30]. A more recent study by Tsahalina *et al.* from the Royal Marsden Hospital in London showed that early postoperative feeding was safe and well tolerated in 22 patients with recurrent gynaecological cancer [31]. However, only four patients with ovarian cancer were part of this study and all but one patient (nasogastric feed) had the feeds delivered through a gastrostomy or a jejunostomy. The focus of the latter study was on safety, and the former on effectiveness of postoperative nutrition.

Considering the above one could argue that enteral feeding should be part of current standard care in the management of advanced EOC. By contrast and when the trial was initiated and started enrolling patients it was not practised in any of the Australian gynaecological oncology units as a

matter of policy. Reasons for not accepting enteral feeding as standard care included: a. Lack of need (oral diet will typically resume within 10 days of surgery); b Possible complications (aspiration of feeds and subsequent chemical pneumonitis, discomfort and irritation, diarrhoea); c. Costs (approximately $10 per day for the feeds plus the involvement of a nutrition team); and d. Lack of efficacy data.

Hence, this trial was meant to address the above objections.

QoL outcomes

Similar to findings from a prospective study examining QoL outcomes in head and neck cancer patients receiving home enteral tube feeding after surgery, our study found improved QoL scores from baseline to 6 weeks postoperatively in both groups, with no difference between the groups [32]. Another randomised clinical trial (RCT) examining preoperative enteral feeding versus no preoperative enteral feeding in severely malnourished head and neck cancer patients however, found significantly improved QoL in patients receiving intervention [33]. In this trial feeding commenced prior to start before surgery to condition patients for the physical stress.

The primary endpoint was chosen to be QoL because it is a reliable and important outcome in oncology[26]. However, given the extensive impact that surgery and/or chemotherapy has on patients' wellbeing, the difference that the nutritional intervention made might have been small. Future studies may wish to consider using a more proximal main endpoint such as return to activity or return to self-care.

Length of hospital stay

Contrary to studies that demonstrated a decreased LOS in a mixed cohort of gynaecologic oncology patients undergoing surgery that received early oral feeding, and a meta-analysis in a mixed cohort of surgical patients showing decreased LOS receiving early enteral versus parenteral nutrition [6, 34], our study did not demonstrate any difference in LOS between treatment arms. Anecdotally, weaning patients off the enteral feeds added an additional layer of complexity to the management of these already complex cases and may have taken additional time.

Adverse events

Also contrary to two meta-analyses of comparing enteral feeding with TPN in a group of mixed surgical patients [34, 35], we did not find any differences in surgical complication rates between patients who did or did not receive enteral feeding. Postoperative 30-day mortality included one death in the control group and none in the intervention arm. Our trial was not designed to follow patients long-term and hence, survival was not studied.

Strengths of our study include the study design as a prospective randomised clinical trial, that participants were recruited at multiple centres and thoroughly assessed for nutritional status. Limitations of the study include that masking was not possible; that a significant proportion of the intervention arm did not receive the intended nasojejunal tube or enteral feeds; a few patients enrolled were found not to have a malignancy. However, this may reflect usual limitations that will also be encountered in clinical practice with delivery of enteral feeding and treatment of suspected EOC. Another limitation is that the trial lost a significant number of patients from QoL assessment at the 6-week (n=27) and post-chemotherapy (n=50) follow-up period, likely reflecting the high morbidity of patients with advanced EOC; thus it is possible that QoL functionality may have been overestimated among participants remaining in the trial at these follow-up periods.

Overall, enrolment into this trial was “slow”. Firstly, we noticed that a large number of patients declined participation in the trial because they were uncomfortable with the prospects of a foreign body placed in their pharynx over a number of days.

Secondly, from 2010 onwards the five sites involved adopted a protocol of neoadjuvant therapy for patients who were deemed at high risk for severe adverse events following surgical cytoreduction [36, 37]. The association of malnourishment with the risks of surgical complication has been established previously [6] and hence, malnourished patients were more likely to receive neoadjuvant chemotherapy than upfront surgery. Commonly, patients would recover from malnourishment during neoadjuvant chemotherapy. Consequently, fewer malnourished patients, who are the subject of this study, could be identified and enrolled in this study. Only patients with

moderate to severe malnutrition were included in the study, however, patients treated with neoadjuvant therapy had evidence of better baseline nutritional status as measured by PG-SGA score compared with patients not treated with neoadjuvant therapy (11.0 vs. 13.7, p 0.03). A comparable number of patients in each treatment arm were treated with neoadjuvant therapy, thus we do not expect the effect of neoadjuvant therapy on nutritional status to have affected results from analyses reported in this paper.

One of the main eligibility criteria included proven or suspected advanced ovarian cancer. In our sample we had patients overrepresented with suspected ovarian cancer on whom the diagnosis of ovarian cancer was not confirmed and a benign or ovarian borderline tumour or other histology were diagnosed on subsequent histopathology. When intention-to-treat analysis was performed exluding these 27 patients, we found evidence of improved physical well-being at post-chemotherapy follow-up in the intervention versus the control arm (23.1 vs 20.6, p 0.04), indicating that QoL recovery may be better secondary to improved nutrition from early enteral feeding. No significant differences were found between arms in other QoL measurements or PG-SGA score at baseline or follow-up in this analysis.

It is possible that the presence and duration of NJ tube insertion may have impacted on perioperative QoL. In this trial we did not collect QoL measurements during the immediately postoperative period thus we are unable to assess the impact of the presence of an NJ tube on QoL.

In summary, this trial shows that in patients with EOC, early enteral feeding may improve nutritional status but does not significantly improve patients' quality of life compared to standard of care.

CONFLICTS OF INTEREST

OA has been an occasional adviser for Genzyme, with honoraria for presentations. OA has received research support from Bristol-Myers Squibb. All other authors declared no conflicts of interest.

ACKNOWLEDGEMENTS

We acknowledge clinical trial staff involved in the OPEN trial, including Trudi Cattley (Clinical Research Manager), Dana Middleton (Trial Manager), Michaela Clifford (Trial Manager and

Dietician), Merrilyn Banks (Dietician), Srinivas Kondalsamy-Chennakesavan (Investigator), Clinical Trial Coordinators: Noel Lipscombe, Samantha Gray, Kate Russell, Genevieve Skinner, Georgina Gower and Kerry Millgate, and Monitors: Vanessa Behan and Anne Hughes.

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448 Table 1: Demographic and clinical characteristics by treatment group (intention-to-treat analysis)

Demographic characteristics	**Intervention**	**Control**
	N=53	N=56
Age in years, mean(SD)	61.8 (11.4)	63.7 (12.7)
BMI category†		
Underweight	7 (13%)	3 (5%)
Normal	16 (30%)	16 (29%)
Overweight	18 (34%)	21 (37.5%)
Obese I	9 (17%)	9 (16.1%)
Obese II	1 (2%)	2 (4%)
Obese III	2 (4%)	5 (9%)
Education		
Completed 12 years of school or less	38 (72%)	37 (66%)
Completed >12 years of school	11 (21%)	12 (21%)
Employment		
Retired	25 (47%)	22 (39%)
Employed full-time	8 (15%)	10 (18%)
Employed part-time or casual	5 (9%)	4 (7%)
Other	13 (25%)	10 (18%)
Marital status		
Married or living together	32 (60%)	22 (39%)
Other	17 (32%)	23 (41%)
Private health insurance		
Yes	14 (26%)	10 (18%)
No	34 (64%)	36 (64%)
Income		
Less than AUS $40,000	23 (43%)	21 (37%)
AUS $40,000+	12 (23%)	14 (25%)
Not answered	18 (34%)	21 (37%)
Birth country		
Australia	37 (70%)	39 (70%)
Other	15 (28%)	10 (18%)
Clinical characteristics		
ECOG performance status		
0	13 (25%)	10 (18%)
1	24 (45%)	28 (50%)
2 or more	16 (30%)	18 (32%)
Surgical stage*		
Stage 1	2 (4%)	9 (16%)
Stage 2	1 (2%)	2 (4%)
Stage 3	24 (45%)	24 (43%)
Stage 4	13 (25%)	7 (13%)
Node dissection performed		
Yes	17 (32%)	17 (30%)

No	36 (68%)	39 (70%)
Hospital stay‡		
5 days or less	2 (4%)	4 (7%)
>5 days	50 (94%)	51 (91%)
Pathological characteristics		
Grade of differentiation		
Grade 1 (well differentiated)	-	6 (11%)
Grade 2 (moderately differentiated)	1 (2%)	3 (5%)
Grade 3 (poorly differentiated)	29 (55%)	26 (46%)
Benign	5 (9%)	8 (14%)
Borderline/Other	18 (34%)	13 (23%)
Histological type**		
Serous	25 (47%)	30 (53%)
Mucinous	4 (8%)	3 (5%)
Metastatic	9 (17%)	3 (5%)
Other	6 (11%)	9 (16%)
Chemotherapeutic characteristics		
Neo-adjuvant chemotherapy		
Yes	18 (34%)	16 (29%)
No	35 (66%)	40 (71%)
Adjuvant chemotherapy		
Yes	42 (79%)	39 (70%)
No	11 (21%)	17 (30%)

SD=standard deviation. Reported percentages are for total number of 53 for intervention and 56 for control group. Numbers do not always add up to 109 because of missing demographic data. †Based on WHO categories. *Surgical stage is missing for 13 patients with benign and 7 patients with borderline histology and 7 with other histologies including clear cell histology. **Histological type is not reported for 13 patients with benign and 7 patients with borderline histology. ‡Hospital stay is not reported for 2 patients that did not receive surgery.

457 Table 2: Mean Patient-Generated Subjective Global Assessment (PG-SGA) Score over time (intention-
458 to-treat analysis)

	Intervention	Control	P value
Baseline	N=53	N=56	
PG-SGA score, mean(SD)	12.8 (5.6)	13.0 (6.1)	0.94
PG-SGA Global			
A	13 (25%)	9 (16%)	0.53
B	36 (68%)	43 (77%)	
C	4 (8%)	4 (7%)	
7 days postoperatively	N=50	N=53	
PG-SGA score, mean(SD)	11.8 (5.6)	13.9 (5.2)	<0.05
PG-SGA Global			
A	11 (22%)	6 (11%)	0.28
B	35 (70%)	40 (75%)	
C	4 (8%)	7 (13%)	
6 weeks postoperatively	N=48	N=49	
PG-SGA score, mean(SD)	7.7 (5.3)	8.6 (5.4)	0.42
PG-SGA Global			
A	24 (50%)	23 (47%)	0.92
B	21 (44%)	22 (45%)	
C	3 (6%)	4 (8%)	
Post-chemotherapy	N=36	N=35	
PG-SGA score, mean(SD)	7.1 (5.2)	6.4 (5.1)	0.41
PG-SGA Global			
A	26 (72%)	24 (69%)	0.28
B	8 (22%)	11 (31%)	
C	2 (6%)	-	

459 PG-SGA=Patient-Generated Subjective Global Assessment, SD = standard deviation

460

461 Table 3: Quality of life over time and 7 day postoperative outcomes (intention-to-treat analysis)

	Intervention	Control	P value
Baseline	N=53	N=56	
FACT-G	72.9 (14.2)	68.5 (16.2)	0.18
FACT-O	94.5 (21.0)	89.0 (19.6)	0.19
EQ5D Index	0.70 (0.20)	0.65 (0.22)	0.25
Euroqol-VAS	60 (23)	51 (20)	0.03
6 weeks postoperatively	N=38	N=44	
FACT-G	82.0 (15.5)	76.3 (14.2)	0.09
FACT-O	108.4 (20.7)	100.9 (21.7)	0.12
EQ5D Index	0.78 (0.22)	0.76 (0.15)	0.63
Euroqol-VAS	69 (20)	61 (21)	0.08
Post-chemotherapy	N=32	N=27	
FACT-G	85.7 (12.9)	81.8 (13.2)	0.26
FACT-O	113.7 (15.4)	109.5 (18.5)	0.34
EQ5D Index	0.85 (0.13)	0.78 (0.16)	0.06
Euroqol-VAS	72.8 (15.2)	65.2 (19.2)	0.08
At 7 days postoperatively	N=53	N=56	
ICU or HDU admission, N(%)	25 (47%)	19 (34%)	0.16
Nausea/vomiting, N(%)	36 (68%)	39 (70%)	0.85
Blood transfusion, N(%)	21 (40%)	24 (43%)	0.73
Protein intake, median(range)	52 (0-5495)	44.5 (0-138)	0.15
Energy intake, median(range)	3848 (0-9313)	3463 (0-8518)	0.46
Pain score, median(range)	2 (0-7)	2 (0-8)	0.83
Pain score, mean(SD)	2.5 (1.9)	2.5 (2.2)	0.96

462 FACT-G=Functional Assessment of Cancer Therapy-General, FACT-O =Functional Assessment of
463 Cancer Therapy-Ovarian, EQ5D=EuroQoL 5D, VAS=Visual Analogue Score, ICU=Intensive Care Unit,
464 HDU=High Dependency Unit, N=number, SD=standard deviation.

465

466 Figure 1: OPEN trial CONSORT Flow Diagram

467

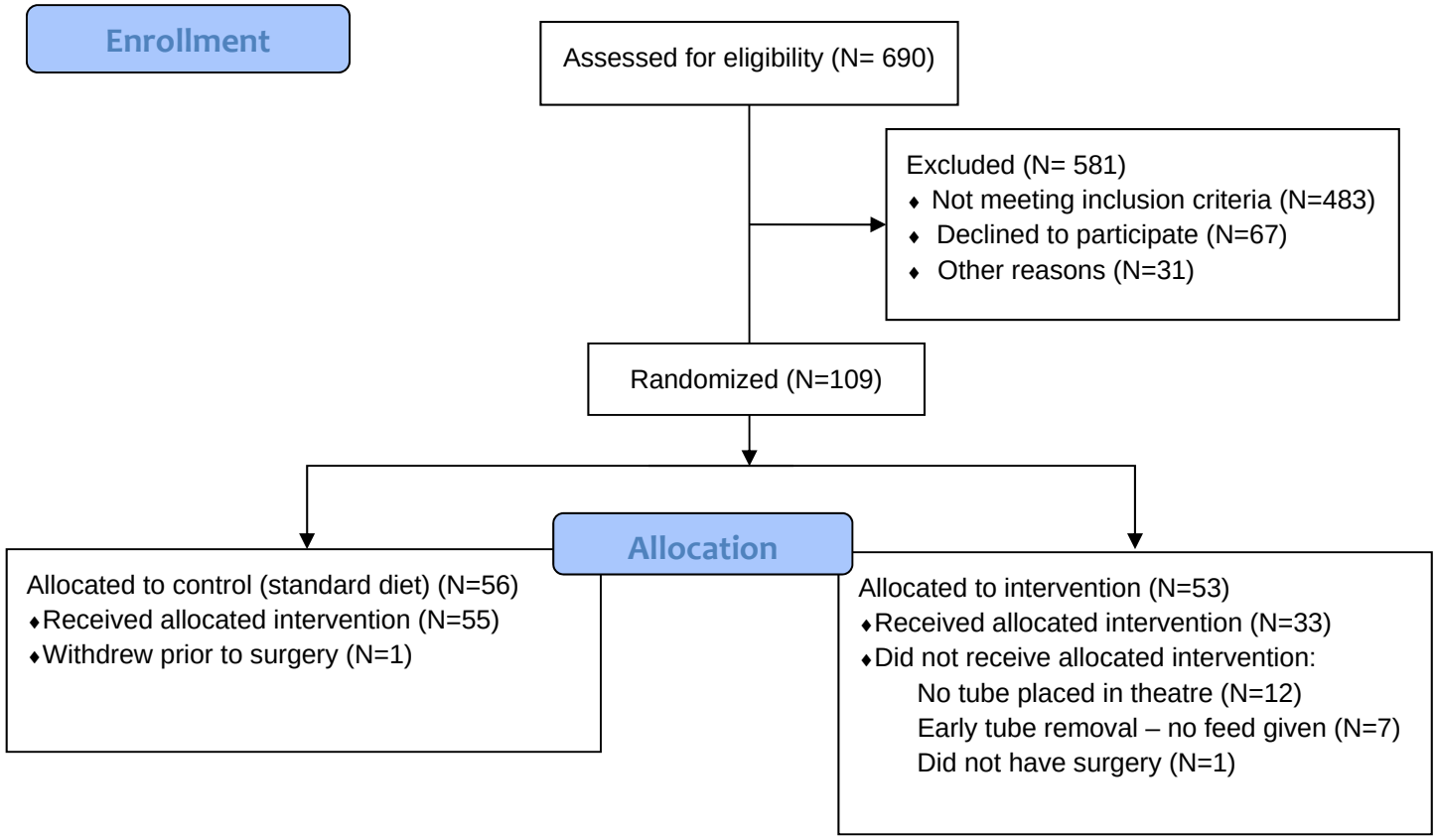

Figure 2: Distribution of hospital length of stay for each treatment arm